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Medical technology consultation: gammaCore for cluster headache

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
4. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
5. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
6. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
7. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

Title: MT323 Gammacore for Cluster Headaches

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
cCH	Chronic Cluster Headache
CI	Confidence interval
CH	Cluster Headache
DH	Department of Health
EAC	External Assessment Centre
EHF	European Headache Federation
eCH	Episodic Cluster Headache
ICHD	International Classification of Headache Disorders
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
nVNS	Non-invasive Vagus Nerve Stimulation
ONS	Occipital nerve stimulation
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
rCCH	Refractory Chronic Cluster Headache
RCT	Randomised Controlled Trial
SD	Standard deviation
SPG	Sphenopalatine ganglion stimulation
VAS	Visual Analogue Scale
vs	Versus

1 Executive Summary

The company submission included clinical evidence from 7 published studies (3 randomised trials and 4 cohort studies) and 2 unpublished abstracts. The EAC did not identify any additional studies for inclusion.

The quality of the published evidence ranged from moderate to very low for each of the outcomes of interest and the EAC highlighted some methodological issues to be considered.

Evidence suggests that patients may benefit from the addition of GammaCore to the treatment options available for cluster headache however due to the limitations of the evidence it is not clear whether that benefit is realised for treatment refractory patients or whether the addition of GammaCore to current standard of care confers a benefit in combination with other treatments. GammaCore was used as an adjunct to standard care for prophylactic treatment of cluster headaches in one randomised trial. It was used as acute treatment for the relief of cluster headache attack symptoms in addition to patients' standard prophylactic regimen in two randomised trials and one cohort study. GammaCore was also used as sole treatment for treatment refractory patients in two cohort studies. The EAC concludes that although the published evidence consistently reports a benefit of gammaCore with only one study reporting no benefit, the differences between study methodologies and populations make it difficult to determine the extent and certainty of any benefit.

The company identified three cost utility models in chronic cluster headache populations. The EAC identified two additional models for cost-effectiveness of gammaCore. The five studies were excluded as their findings are not directly applicable. The company submitted a de novo cost model using data from a published trial, the results of which suggest that gammaCore was cost saving when considering patients with chronic cluster headache. The EAC agreed with the model structure and did not make any changes to the company base case. The EAC noted that the model is highly dependent on an initial free trial period and reducing the use of abortive medication. Although there are some uncertainties about the data, there is currently not an alternative robust data source that could be used.

2 Background

2.1 Overview and critique of company's description of clinical context

The background and clinical context provided by the company was sufficiently detailed and informative. The EAC noted a minor error in the last paragraph of section 3.1 where the pain free period for episodic cluster headaches was described as being one month when in fact the pain free period for episodic cluster headaches is at least 3 months according to the International Classification for Headache Disorders (ICHD).

The company submission states that cluster headaches affect 0.1% of the population in the UK however the EAC could find no reference to this figure. Fischera et al. (2008) investigated the prevalence of cluster headache and reported that 1 year prevalence rates ranged from 0.003% (3/100,000) to 0.15% (150/100,000) and lifetime prevalence rates ranged from 0.056% (56/100,000) to 0.4% (381/100,000). Pooled analysis suggested a worldwide lifetime prevalence of 0.12% (124/100,00) and a 1 year worldwide prevalence of 0.05% (53/100,000). None of the studies included in Fischera et al. (2008) were UK based and no UK specific prevalence data was identified by the EAC. One clinical expert suggested that they treat 150 patients per year (30 episodic and 120 chronic cluster headache patients) and that there were no patients with cluster headache who were not being treated, suggesting that the UK prevalence for this condition is indeed low.

The EAC considers that the estimated prevalence reported in the company submission is appropriate, representing a conservative estimate of the incidence of cluster headaches in the UK.

2.2 Critique of company's definition of the decision problem

Table 1: Critique of company's definition of decision problem

Decision Problem	Company Submission	Matches Decision Problem (Y/N)	EAC Comment
Population	People over the age of 18 years with cluster headache for whom standard care is ineffective or contraindicated	Y	Cluster headache can be either episodic or chronic and both subtypes are included in the scope.
Intervention	gammaCore	Partially	The technology under investigation is stated as being gammaCore and gammaCore Sapphire. GammaCore is the original device which comes pre-loaded and needs to replaced when finised. GammaCore sapphire is an upgraded model which can reloaded by replacing a card in the device. GammaCore Sapphire can also be recharged using a mains plug whereas the previous version could not. The manufacturers state that the mechanism of action for vagus nerve stimulation is the same for both devices and that the older gammaCore device has almost been phased out of use in the NHS. The EAC consider the two devices to be essentially the same for the purposes of this report. The technology will be referred to as gammaCore throughout the report.
Comparator	• Subcutaneous or nasal spray triptan therapy (acute) • Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute) • Verapamil (preventive) • Sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache) • Occipital nerve block (preventive)	Y	Although the submission matches the decision problem as laid out in the scope, the EAC notes that some of these are not comparaters in the true sense as the clinical pathway states that gammaCore will be used when these treatments are ineffective for patients (or instead of if contraindicated).
Outcomes	• Frequency, severity, and duration of acute episodes of cluster headache • Time taken to relieve pain of acute episode (acute use)	Y	

	• Average response rate and proportion of patients at 50% and 75% response rates • Number of times device used for daily prevention • Number of times device used for acute treatment • Patient reported pain and disability scores • Patient health-related quality of life, including impact on occupation and employment • Patient satisfaction • Reduction of ECG and blood testing for monitoring of drug treatments • Use of outpatient and healthcare services, including psychiatric care • Device-related adverse events		
Cost Analysis	Costs will be considered from NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Partially	The submitted economic model considered chronic cluster headache only. The rationale given was that UK based evidence suggests only small numbers of patients with eCH are likely to be offered gammaCore in the UK. The following were not included in the model as comparators: • Verapamil (preventive) • Sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache) • Occipital nerve block (preventive) This is discussed in the economic section.
Subgroups	• Acute treatment of cluster headache • Prevention of cluster headache • Episodic cluster headache • Chronic cluster headache	Y	

2.1 Special considerations, including issues related to equality

People with cluster headache are likely to be described as disabled because it is a chronic condition that is likely to last longer than 1 year. This technology

has the potential to avoid invasive treatments (such as sphenopalatine ganglion nerve stimulation implants) or the use of unlicensed medications with potentially serious side effects.

Self-administration of treatment with gammaCore requires manual dexterity and the ability to follow instructions. GammaCore cannot be used by people with cochlear implants or pacemakers and should not be used in people who are pregnant, lactating, or under 18 years.

The EAC consider there to be no specific equality issues relating to the use of gammaCore in addition to those highlighted in the scope. Regarding the issues highlighted in the scope, the EAC suggests that these should be considered by the prescribing clinician in consultation with the patient before commencing use of the gammaCore device and where possible address specific issues which could be overcome to facilitate use of the gammaCore device (e.g. manual dexterity issues could be overcome by finding an alternative approach to administration such as help from a family member).

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The EAC consider that the search strategy submitted was adequate although not comprehensive, in particular it lacked medical subject headings. Searches were only conducted in databases required by the MTEP submission template i.e. Medline, Medline In Process, Embase and The Cochrane Library. The company submission included searches for unpublished literature, ongoing clinical trials and clinical data on safety and adverse events of gammaCore. To ensure that all relevant evidence had been identified and presented the EAC undertook their own literature search, details are in appendix A.

3.2 Critique of the company's study selection

The company submission description of the clinical pathway states that gammaCore is intended to for use in patients with cluster headaches for whom standard treatment in not tolerated or does not work (section 3.3).

Treatment refractory chronic cluster headache (rCCH) are chronic cluster headaches (according to ICHD-3 beta criteria) with at least 3 severe attacks

per week that impact patients' quality of life despite prophylactic (preventative) or acute (symptomatic) treatment which have failed consecutive prophylactic treatment trials with at least three agents that showed efficacy over placebo in randomized controlled studies, used at the maximum tolerated dose over a sufficient period of time (Mitsikostas et al 2014). Information from one clinical expert supported this definition.

Treatment refractory patients were specifically identified in only two non-comparative studies (Marin et al. 2018 and Trimboli et al. 2018) which were using gammaCore after other treatments had failed. One non-comparative study included both treatment refractory and non-refractory patients (Nesbitt et al. 2015).

One randomised open label study (Gaul et al. 2016) states in the discussion that included patients were treatment refractory however the study inclusion/exclusion criteria does not make this explicit and the abstract states that the study compared adjunctive prophylactic nVNS suggesting patients were not refractory to alternative prophylactic treatments nor were these alternative treatments necessarily contraindicated.

In both the ACT 1 and ACT 2 trials (Silberstein et al 2016; Goadsby et al 2018) more than 60% of participants were receiving prophylactic treatment at baseline and GammaCore was being assessed as an acute treatment.

One clinical expert stated that gammaCore should be considered similarly to Botox and only provided to patients who have failed three treatments while one expert suggested that anyone might benefit but particularly patients in whom drugs have failed or are contraindicated. One clinical expert stated that gammaCore was being used specifically in medically refractory patients. Two clinical experts stated that gammaCore is being used both acutely and prophylactically in cluster headache patients and another clinical expert stated that is could be used alongside current acute and prophylactic treatment.

Based on the information from clinical experts and the published evidence, it is possible that the place for gammaCore in the clinical pathway may require some further discussion.

3.3 Included and excluded studies

The company clinical submission appears to include a total of six published studies (Silberstein et al. 2016, Goadsby et al. 2018, Gaul et al. 2016, Nesbitt et al. 2015, Marin et al. 2018 and Trimboli et al. 2018) and two conference abstracts (deCoo et al. 2017 and Gaul et al 2018)

The company submission makes reference to results from additional analyses of the PREVA data in section 7.4.2 (Gaul et al. 2018, Gaul et al. 2017 and Morris et al. 2016) however these do not appear to be included in the PRISMA diagram or in tables B3 and B4 (list of relevant published and unpublished studies). The EAC noted that the company submission appears to treat all publications relating to the PREVA trial (Gaul 2016) as a single entity and has therefore not included separate data extraction tables or critical appraisals for these additional sources. While the EAC acknowledges that the primary publication for the PREVA trial (Gaul 2016) is likely to represent the most comprehensive and important data from the trial, the EAC considers that as Gaul et al. 2017 was a post-hoc analysis of the trial data, it should be considered a cohort study and appraised it as such. Details of the conference abstract (Gaul et al. 2018) should also be included in a manner so as to make it clear that it represents additional analysis not included in the primary trial analysis. The EAC has added a data extraction table for both Gaul et al. 2017 (table 2 and appendix B and Gaul et al. 2018 (table 3) and a CASP critical appraisal checklist for Gaul et al. 2017 (appendix D)

The company submission included unpublished data from a pooled analysis of the ACT 1 (Silberstein et al. 2016) and ACT 2 (Goadsby et al. 2018) which is referenced as deCoo 2019 throughout the submission. The EAC note that searches did not identify a 2019 publication only a 2017 abstract. In addition the reference list of the company submission only lists de Coo et al. 2017. Discussion with the manufacturer indicated that the deCoo et al 2017 conference abstract is the only publically available source of data at the current time.

The EAC did not identify any additional studies for inclusion in the assessment report.

A summary of the studies included by the EAC is presented in table 2, table 3 and table 4. Only the results for the double blind phase of the ACT 1 (Silberstein 2016) and ACT 2 (Goadsby 2018) and for the initial randomised phase of the PREVA study (Gaul 2015) are presented. For full results including the open label and extenstion phases of these studies see appendix B.

Details of adverse events are reported in section 3.7 and summarised in table 5.

Included and Excluded Studies

Table 2: Published Studies

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Silbserstein et al (2016)	Double blind randomised control trial followed with an open label period NCT01792817 (ACT1) nVNS using gammaCore + standard care (SoC) versus sham + SoC nVNS protocol: 3 consecutive 2 minute stimulations to the right side of the neck at the onset of premonitory symptoms of pain During double blind phase: Up to 5 attacks treated with only one per 12 hour period Abortive/pain relieving rescue medications were permitted no sooner than 15	Participants 18 – 75 years, n=150, with either episodic (eCH) n=101 or chronic (cCH) cluster headache (CH) n=49nVNS + SoC: n=73 (eCh: 50, cCH: 23) (n=60 ITT), mean age (SD) = 47.1yrs (13.5), male = 59 (81%). Sham + SoC: n=77 (eCH: 51, cCH: 26) (n=73 ITT), mean age (SD) = 48.6yrs (11.7), male = 67 (87%). 20 centres in the USA Conducted February 2013 to October 2014 ● Clinical Pathway: GammaCore used as an additional acute treatment option Population: Not treatment refractory, 68% were using	Primary Outcome Response (defined as proportion of patients achieving a pain intensity score of 0 or 1 at 15 minutes after treatment initiation for first attack. (Rescue medication use within 60 minutes was considered a treatment failure) Secondary Outcomes Sustained treatment response (proportion of participants with a pain intensity score of 0 or 1 without rescue medication at 15-60 minutes	***Response Rates*** • All CH: 26.7% (nVNS) versus 15.1% (Sham), p=0.1 • eCH: 34.2% (nVNS) versus 10.6% (Sham), p=0.008 • cCH: 13.6% (nVNS) versus 23.1% (sham), p=0.48 Sustained Response • All CH: 26.7% (nVNS) versus 12.3% (sham), p=0.04 • eCH: 34.2% (nVNS) versus 10.6% (sham), p=0.08 • cCH: 13.6% (nVNS) versus 14.5% (sham), p=1.0 Pain intensity at 15 minutes	nVNS +SoC 14 discontinuations from double blind to open label phase 3 Nonadherence 8 No CH/CH ended 2 Loss to follow up 1 other	Results reported for the double blind randomised period Study was not powered for sub-group analysis Treatment adherence to prescribed nVNS has not been reported. Patient reported outcomes. Some baseline differences: Twice the number of eCH patients compared with cCH patients in population. • Greater proportion of nVNS patients were experencing longer length CH attacks, 34%

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	minutes after each nVNS initiation. ●	prophylactic treatment at baseline	after treatment initiation for CH attack) Average of all participants mean pain intensities at 15 minutes after treatment initiation for all attacks (up to 5 attacks per participant). *Safety Endpoints* Serious adverse device effects (SADEs) ●	• All CH: 2.1 [95% CI 1.8-2.3] (nVNS) versus 2.0 [95% CI 1.8-2.2] (sham), p=0.4. • eCH: 2.0 [1.8-2.3] (nVNS) versus 2.0 [1.8-2.3] (sham), p=1.0 • cCH: 2.3 [1.9-2.6] (nVNS) versus 1.9 [1.6-2.3] (sham), p=0.2 Responders at 15 mins for ≥50% of treated attacks • All CH: 26.7% (nVNS) versus 20.6% (Sham), p=0.41 • eCH: 34.2% (nVNS) versus 14.9% (sham), p=0.04 • cCH: 13.6% (nVNS) versus 30.8% (sham), p=0.19 Pain free at 15 minutes for ≥50% of treated attacks • All CH: 11.7% (nVNS) versus 6.9% (sham), p=0.33		more differences in medication Study was sponsored by the company with data analysis funded by the company One of the authors is an employee of the company.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				• eCH: 15.8% (nVNS) versus 2.1% (sham), p=0.04 • cCH: 4.6% (nVNS) versus 15.4% (sham), p=0.36 Duration of first CH attack (mins) • All CH: 50.6±38.3(nVNS) versus 59.9±47.5 (sham), p=0.25 • eCH: 48.4±35.4 (nVNS) versus 61.2±49.5 (sham), p=0.21 • cCH: 54.5±43.8 (nVNS) versus 57.6±44.8, p=0.82 Change in duration of attacks from baseline to first attack (mins) • All CH: -9.5±51.8 (nVNS) versus 12.8±45.5 (sham), p=0.03 • eCH: -14.4±59.5 (nVNS) versus		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				16.3±51.5 (sham), p=0.03 • cCH: 1.0±28.6 (nVNS) verus 5.4±29.2 (sham), p=0.69 Rescue medication use in the first 60 mins after treatment initiation • All CH: 38.3% (nVNS) versus 50.7% (sham), p=0.15 • eCH: 42.1% (nVNS) versus 48.9% (sham), p=0.53 • cCH: 31.8% (nVNS) versus 53.9 (sham), p=0.13		
Goadsby et al (2018)	Double blind randomised control trial followed with an open label period NCT01958125 nVNS using gammaCore + standard care (SoC) versus sham + SoC	Participants ≥ 18 years of age, n=102 patients with eCH (n=30) or cCH (n=72) nVNS+SoC: n=50 (eCH: 15, cCH 35) (n=48 ITT), mean age (SD) = 43.9yrs (10.6), male= 35 (70%). Sham + SoC: n=52 (eCH: 15, cCH: 37) (n=44 ITT) mean age (SD) = 46.9yrs (10.6), male= 38 (73%)	Primary Outcomes Proportion of all treated attacks achieving pain free status within 15 minutes after treatment initiation. Secondary Outcomes	*Pain free status within 15 minutes* • All CH: 14% (nVNS) versus 12% (sham), p=0.71 • eCH: 48% (nVNS) versus 6% (sham), p<0.01 • cCH: 5% (nVNS) versus 13% (sham), p=0.13	nVNS +SoC double blind phase 2 Missing diary 1 Protocol Violation 2 other Open label phase 2 discontinued (1 AE, 1 other)	Results reported for the double blind period. No details of how randomisation sequence generated. Twice the number of cCh patients compared with eCH patients in population.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	nVNS protocol 3 consecutive 2 minute stimulations ipsilateral to their CH attack at the time of attack onset. 3 additional stimulations permitted if attack was not aborted within 9 minutes of treatment initiation. Subjects were asked to refrain from using rescue treatments (medications and/or inhaled oxygen) for 15 minutes after beginning stimulation A minimum of 6 hours between nVNS treatments was required. ●	9 tertiary care centres across 4 European Countries including the UK (N=52 UK patients from clinicaltrials.gov) Conducted September 2013 to October 2014 ● Clinical Pathway: GammaCore used as an additional acute treatment option Population: Not treatment refractory, 61% of participants were using prophylactic treatment at baseline	Proportion of treated attacks per subject achieving responder status within 30 minutes Proportion of treated attacks per subject achieving pain free status within 30 minutes Mean change in pain intensity from attack onset to the 15 and 30 minute timepoints Patients achieving pain free status and responsder status in ≥50% of treated attacks Adverse events and adverse device effects ●	*Odds Ratios (95% CI) from the GEE model (adjusted for site in the total cohort and in the cCH subgroup)* **All CH:** 1.22 (0.42-3.51), p=0.71 **eCH:** 9.19 (1.77-47.8), p<0.01 (not adjusted for site) **cCH:** 0.41 (0.13-1.30), p=0.13 *Treated Attacks achieving responder status within 30 minutes* • All CH: 43% (nVNS) versus 28% (sham); p=0.05 • eCH: 58% (nVNS) versus 28% (sham); p=0.07 • cCH: 37% (nVNS) versus 29% (sham); p=0.34 *Treated attacks achieving pain free status within 30 minutes*	SoC+Sham double blind phase 8 exclusions (6 missing diary, 2 no attacks treated) 6 discontinued (2 withdrawal, 2 loss to follow up, 2 AE) Open label phase 2 loss to follow up	Study did not reach required sample size for power of primary outcome. Study was not powered for subgroup analysis Study was sponsored by the company with data analysis funded by the company One of the authors is an employee of the company

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				• All CH: 26% (nVNS) versus 18% (sham); p=0.17 • eCH: 43% (nVNS) versus 19% (sham); p=0.08 • cCH: 19% (nVNS) versus 18% (sham); p=0.76 *Mean decreases in pain intensity from attack onset at 15 and 30 mins (nVNS vs. sham)* • All CH: 15 mins: -1.3 (0.02) versus -0.9 (0.1); p=0.06 • 30 mins: -1.6 (0.2) versus -1.2 (0.2); p=0.07 • eCH: 15 mins: -1.7 (0.4) versus -0.6 (0.2); p=0.01 • 30 mins: -1.9 (0.4) versus -0.8 (0.4); p=0.03 • cCH:15 mins: -1.2 (0.2) versus -1.0 (0.2); p=0.52 • 30 mins: -1.5 (0.2) versus -1.3 (0.2); p=0.5		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				Patients achieving pain free status in ≥50% of treated attacks after 15 mins • All CH: 17% (nVNS) versus 7% (sham), p=0.15 • eCH: 36% (nVNS) versus 8% (sham), p=0.16 • cCH: 9% (nVNS) versus 7% (sham); p=1.00 *Patients achieving responder status for ≥50% of treated attacks after 15 mins* • All CH: 40% (nVNS) versus 14% (sham); p<0.01 • eCH: 64% (nVNS) versus 15%; p<0.01) • cCH: 29% (nVNS) versus 13% (sham); p=0.11		
Gaul et al (2016)	Randomised, multi-centre, open label, parallel group study. NCT: 01701245	Participants 18- 70 years with chronic CH; n=114 with n=97 randomised (n=24 UK participants from clinicaltrials.gov).	Primary Outcomes • Reduction in the mean number of CH attacks	*Effect of nVNS on CH attack frequency* nVNS+SoC showed a greater reduction from baseline compared with	nVNS Randomised Phase 4 withdrawals	Study was funded by the company

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	nVNS+SoC versus SoC alone. nVNS protocol: • Mandatory prophylaxis of three 2 minute stimulations (i.e. three doses) five minutes apart administered twice daily (i.e. six doses per day) to the right side of the neck (right vagal nerve). Participants also had the option of acutely treating CH attacks with three additional nVNS doses at pain onset but were advised to not administer prophylactic therapy within a two-hour period after acute treatment Abortive or pain-relieving medication	nVNS+SoC n=48 (n=45 ITT), mean age (SD) = 45.4 yrs (11.0), male= 34 (71%); SoC n=49 (n=48 ITT mean age (SD) = 42.3yrs (11.0), male= 33 (67%). 10 European sites including 3 in the UK. Conducted October 2012 to March 2014. ● Clinical Pathway: GammaCore used as an additional prophylactic treatment option rather than after treatment failure Population: Not treatment refractory, 53% of participants were using Verapamil/verapamil hydrochloride at baseline. There was a smaller percentage of participants using other prophylactic treatments.	per week, defined as the number of attacks during the last two weeks of the randomised phase minus the number of attacks during baseline divided by 2. Secondary Outcomes: • Reductions in mean number of CH attacks per week during the last 2 weeks of the extension phase • Response Rate: Proportion of patients with	SoC alone: -5.9 (SE, 1.2) versus -2.1 (SE, 1.2) giving a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI 0.5-7.2; p=0.02) *≥50% Response Rates* Response rate was significantly higher in the nVNS+SoC group compared with SoC alone: 40% (18/45) versus 8.3% (4/48); p<0.001) *Abortive Medication Use* A 57% decrease in the frequency of abortive medication use was noted in the nVNS+SoC group (Δ= -15 (95% CI: -22.8 to -7.2), p<0.001) compared with (Δ= -2 (95% CI: -9.4 to 5.4), p=0.59) in the control arm (% decrease NR). Changes in abortive medication use were driven by reductions in use of SC sumatriptan (p=0.007) and	Extension Phase 11 discontinuations (4 withdrawals, 2 loss to follow-up, 1 protocol violation, 3 AEs, 1 other) SoC Randomised Phase 1 discontinuation (did not meet inclusion/exclusion criteria) Extension Phase 11 discontinuations (4 loss to follow up, 1 protocol violation, 2 AEs, 4 other)	One of the authors is an employee of the company No details of how randomisation sequence generated or if concealed. Open label study, outcome assessment not blinded as recorded by patients.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	was permitted at least 15 minutes after initiation of nVNS treatment. Changes in SoC prophylactic medications were not permitted during the study. ●		≥50% reduction in mean number of CH attacks per week (assessed during the last 2 weeks of randomisation and last two weeks of extension phases. • Abortive medication use • Duration and intensity of CH attacks acutely treated with nVNS • Number of CH attacks, CH pain intensity (five point scale), CH duration and abortive medication use (all assessed	inhaled oxygen (p=0.02). These reductions were maintained through the extension phase. *Use of nVNS as abortive therapy* 93.8% (45/48) of participants in the nVNS+SoC arm acutely treated ≥1 CH with nVNS during the randomisation phase. *Quality of Life* *EQ-5D-3L Indexed score changes from baseline* In the mITT population (baseline to randomised), changes from baseline were significantly improved for nVNS+SoC (n=35) compared with SoC alone (n=46) – (nVNS+SoC minus SoC: Δ=0.194 (95% CI 0.054-0.334), p=0.007) The change in EQ-5D-3L index score in the nVNS+SoC group was above the MID (0.074) and		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
			through patient completed diaries) • Quality of Life (EQ-5D-3L and HIT-6) • Adherence to nVNS treatment (assessed by dividing the actual number of doses administered by the prescribed number of doses)	considered clinically meaningful. *EQ-5D-3LVAS score* In the randomised phase, change from baseline VAS score was greater for nVNS+SoC (nVNS+SoC minus SoC: Δ=8.93 points (95% CI 0.47-17.39, p=0.039) *Patient Satisfaction* 65% of participants (62/96) indicated they would recommend the nVNS device. >75% indicated the device was easy to use and >50% reported some degree of satisfaction with nVNS.		
Gaul et al (2017)	Post-hoc analysis of data from a randomised, multi-centre, open label, parallel group study (Gaul et al. 2016).	10 European sites including 3 in the UK N=114 with N=97 randomised (n=24 UK participants from clincialtrials.gov)	Mean weekly attack frequency over time Global percentage change in weekly CH attack frequency from baseline to the end	*Weekly attack frequency* Mean weekly attack frequency was significantly lower with nVNS+SoC compared with SoC alone (p<0.02) from week 2 of the randomised phase through	Refer to previous study (Gaul et al 2016)	As this is a post-hoc analysis the EAC have treated the study as a cohort study for the purposes of critical appraisal. The outcomes reported

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	●	nVNS+SoC n=48 (n=45 ITT) SoC n=49 (n=48 ITT) ● Clinical Pathway: GammaCore used as an additional prophylactic treatment option rather than after treatment failure Population: Not treatment refractory, 53% of participants were using Verapamil/verapamil hydrochloride at baseline. There was a smaller percentage of participants using other prophylactic treatments.	of the randomised phase Response rates. Cut-offs of ≥25%, ≥50%, ≥75% and 100% reductions from baseline in attack frequency were used to define response. ●	week 3 of the extension phase. Attack frequencies were significantly reduced from baseline beginning at week 1 of the randomised phase and continuing through week 4 of the extension phase ($p<0.05$) *Global mean attack frequency* Global mean attack frequency at decreased by 40% from baseline at the end of the randomisation phase in the nVNS+SoC group versus an increase of 1% in the SoC alone group representing a 41% therapeuatic benefit of nVNS ($p<0.001$). *Response Rates* At the end of the randomised phase A significantly higher proportion of patients in the nVNS+SoC group had		were not prespecified in the clinical study protocol. Study was funded by the company One of the authors is an employee of the company

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				attack frequency reductions from baseline (≥25% and ≥50% reduction, p<0.001; ≥75% reduction, p<0.009). 3 patients (8%) in the nVNS+SoC group had a 100% attack frequency reduction versus 0% in the SoC group.		
Nesbitt et al (2015)	Retrospective, non-comparative, cohort study in patients using nVNS. nVNS protocol • Up to 3 consecutive doses to treat an attack acutely. • For preventative use 2 consecutive doses (and in some cases 3) in the morning and late afternoon (approximately 8 hours apart) daily.	Cluster headache patients n=25, n=19 included in analysis (eCH=11/cCH=8), median age (range) = 49 yrs (13-84), male= 11 (58%) Tertiary headache centre in the UK Conducted January to December 2012. ● Clinical Pathway: GammaCore used as an additional treatment option rather than after treatment failure Population: Not all treatment refractory: 7/19 patients were treatment refractory	• Perceived overall change in condition from baseline • Percentage change in other acute medication use: high flow oxygen and parenteral triptans use while using nVNS device • Percentage of attacks they were able to treat acutely • Proportion of treatments able	*Treatment Changes during nVNS* N=4 patients had changes made to baseline treatments during nVNS use • 2 had preventative medication withdrawn (1 commenced methysergide as a substiture and 1 had a pre-existing dose of verapamil increased) • 1 was prescribe high-flow oxygen • 1 discontinued nVNS following a tapering dose of corticosteroids	N=6 patients excluded (2 failure to return signed summaries, 1 loss to follow-up, 1 equivocal diagnosis, 1 no treatable attacks, 1 poor compliance)	The study was funded by the company. Small, non-comparative study. Patient reported outcomes so possibly subject to bias. Possible cohort overlap with Marin et al. 2018.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	●		to terminate within 15 minutes of device use and time to do so ●	Of this group, 3 had already reported positive but sub-optimal improvements using nVNS and 1 reported no change. *Prevention* N=15 patients reported overall improvement in their condition from baseline. The remaining 4 reported their condition remained the same. Results suggest a mean improvement of 48% (±9%) In 5 patients who had extended follow-up mean estimated improvement was 62% (±8%) at 26 weeks and 59% (±6%) at 52 weeks *Acute treatment: nVNS* Patients reported that nVNS aborted attacks in an average 11 mins (±1 min) of initial device application. This response was stable in 5 patients at 26 and 52 weeks.		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				Acute Treatment: Changes in previously used approaches 3 patients stopped using previously used approaches, oxygen (n=2) or sumatriptan (n=1), in favour of nVNS. N=10 patients reduced oxygen use by an estimate mean of 55% (±8%); 3 continued to use the same amount of oxygen and 1 patient reported an increase by 100%. N=3 patients were able to stop using triptans but continued to use some oxygen and 9 patients reduced their use of triptans by a mean of 48% (±6%). *Effects of attack frequency* There was a reported reduction in 24 hour attack frequency with prophylactic		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				nVNS from a mean 4.5 to 2.6, p<0.0005. *Effect on bout duration* 2 patients with eCH reported a shorenting of bout length using nVNS based on average duration of prior bouts. *Adverse Events* No SAEs were reported Two patients reported a side-shifting of attacks One patient reported transient worsening of pain nVNS basaed on average duration of prior bouts.		
Marin et al (2018)	Retrospective, non comparative cohort study in patients using nVNS Initial nVNS dosing was based on established paradigms	Treatment refractory patients with cluster headache (n=29 with cCH, n=1 with eCH), mean age (range) = 47.9 yrs (16-72), male= 11 (37%) 10 clinical centres in the UK.	• nVNS use • Attack frequency, duration and severity (rated on a scale 0-10 scale)	*nVNS Use* n=16 (53%) patients used nVNS exclusively as preventative therapy, n=1 (3%) used it exclusively as acute treatment, n=13 (43%) used it as both	None	Study was funded by the company One author is an employee of the company.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	and titrated as necessary to achieve maximum benefit ●	Conducted May 2012 to March 2016. ●	• Concomitant treatment use • Safety ●	preventative and acute therapy. *Attack Frequencey* Mean (range) attack frequency with SoC was 26.6 (3.8-77.0) attacks/week. This decreased to 9.5 (0-38.5) attacks/wk with SoC+VNS (p<0.01) N=3 patients who had averaged 42-63 attacks/week experienced no attacks during their nVNS evaluation period (1.7 – 13.2 months) *Attack Duration* Mean duration of attacks decreased from 51.9 (5.0-140.0) minutes with SoC alone to 29.4 (2.5-152.5) minutes with SoC+nVNS; p<0.01 (N=25 patients) *Attack Severity* Mean attack severity decreased from 7.8 (3.0-10.0) SoC to 6.0 (1.0-10.0)		Small, non-comparative study. Patient reported outcomes so possibly subject to bias. Possible cohort overlap with Nesbit et al. 2015.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				with nVNS+SoC; p<0.01 (n=18 patients) *Concomitant Treatment Use* Patients used a mean (range) of 0.8 (0-2) preventative treatments before initiation of nVNS versus 0.7 (0-2) after nVNS initiation. Mean (range) number of acute treatments used was 1.8 (1-4) before nVNS initiation versus 1.1 (0-2) after. N=22 patients used triptan injection or nasal spray as acute treatment before nVNS initiation; 9 (41%) stopped and 12 (55%) decreased their triptan use during nVNS treatment N=27 (93%) patients reported using high-flow		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				oxygen as acute treatment prior to nVNS initiation; 9 (33%) stopped and 17 (63%) decreased their use Overall, N= 3 patients were able to manage their condition with preventative pharmacological treatment only and N=4 were able to use nVNS as monotherapy Benefits reported by patients during evaluation included: • Decreased interictal headache pain • No longer being housebound • Ability to return to work or school • Improved sleep • Decreased absenteeism		

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
				• Avoidance of surgery intended to treat CH • Improved quality of life *Safety* No SADEs were reported Observed AEs included redness and muscle soreness at the treatment site.		
Trimboli et al (2018)	Prospective, non comparative cohort study in patients using nVNS nVNS protocol • 2 consecutive nVNS doses (90 seconds each) on one side of the neck or alternating right and left sides, three times a day, as a preventive	Medically refractory patients with chronic cluster headache, n=12, median age (range) = 49.5 yrs, male = 5 (42%). Tertiary headache centre in the UK Conducted January 2014 to August 2016.	• Response Rates (defined as ≥30% reduction in headache days after 3 month treatment) • Change in headache severity including patients subjective impression of change	*Prophylactic Effect* N=1 showed ≥30% reduction in weekly CH frequency at month 3 compared with baseline. This patient also reported a reduction in oxygen use. N=2 reported a slight improvement from baseline N=3 reported no change N=6 reported a worsening in weekly frequency *Abortive Effect*	None	The full study cohort was 42 patients however the study included patients with migraine and other headache types. The results are presented for the 12 patients with CH only. Small, non-comparative study. Patient reported outcomes so possibly subject to bias.

Included studies	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
	stimulation paradigm. • Up to 3 additional consecutive doses before resorting to their usual abortive treatment for acute treatment.		• Treatment compliance • Safety and tolerability	N=0 reported headache relief using nVNS *Treatment Continuation* N=1 patient continued with nVNS for 10 months but reported a worsening of their condition for 3 consecutive months and discontinued treatment *Treatment Compliance* Data for 4 CH patients were available and the authors postulate that 1 patient was non-compliant based on when they requested a replacement device. *Safety* Data for the CH population was not reported separately though no SAEs were reported for the whole population.		The company provided the devices for a three month trial period and were responsible for training patients in the use of the device A number of the authors have received grants from the company

Table 3: Unpublished Studies

Unpublished Studies	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC Comments
deCoo et al (2017)	Pooled Analysis Intervention: nVNS+SoC Comparator: Sham+SoC	Participants in the ACT 1 (Silberstein 2016) and ACT 2 (Goadsby 2018) trials	ACT 1 Primary Outcome: Response (defined as proportion of patients achieving a pain intensity score of 0 or 1 at 15 minutes after treatment initiation for first attack. (Rescue medication use within 60 minutes was considered a treatment failure) ACT 2 Primary Outcome: Proportion of all treated attacks achieving pain free status within 15 minutes after treatment initiation. Proportion of patients with responder status at 15 minutes for ≥50% of attacks	Response (proportion of patients achieving responder status at 15 minutes (per patient, first attack) (Note: ACT1 primary outcome) ***All CH*** nVNS – 31.5% Sham – 20.5% No statistically significant difference ***eCH*** nVNS – 38.5% Sham - 11.7 P<0.01 ***cCH*** nVNS – 25% Sham - 29.8% No statistically significant difference Proportion of all treated attacks that achieved pain free status at 15 minutes (per attack) (Note: ACT2 primary outcome) ***All CH***	Data from a conference poster therefore unable to verify data from each study as different primary outcomes. Appears to be discrepancies in data reported as compared to individual study papers. Individaul studies only powered for each of their primary outcomes. ***Addendum 19/06/2019*** The full publication (deCoo et al 2019) was made available to the EAC following submission of this Assessment Report but prior to publication of the

				nVNS – 13.2% Sham – 8.7% No statistically significant difference ***eCH*** nVNS – 24.1% Sham – 7.3% P<0.01 ***cCH*** nVNS – 6.8% Sham – 10.9% No statistically significant difference Proportion of patients with responder status at 15 minutes for ≥50% of attacks ***All CH*** nVNS – 32.4% Sham – 17.9% No statisitically significant difference ***eCH*** nVNS – 42.3% Sham - 15% P<0.01 ***cCH*** nVNS – 23.2%	final guidance and has been reviewed. See section 3.8 for further details.

				Sham – 21.1% No statistically significant difference	
Gaul et al (2018)	Post-hoc analysis of randomised trial data	Participants in the PREVA randomised trial (Gaul 2015)	Effect of more frequent nVNS use	Acute nVNS use was reported to 1138/1673 attacks Average decrease in mean weekly attack frequency was significantly greater for patients using acute nVNS for ≥76.9% of their attacks -8.5 attacks/week versus -2.1 attacks per week (p<0.01) Using nVNS for <76.9% of attacks showed no significant difference -3.7 attacks/week versus -2.1 attacks per week (p=1.00) Within the nVNS group, mean reduction in weekly attack frequency was greater for patients using ≥8.2 daily stimulations compared with those using <8.2 stimulations but these were difference were not significantly different from the SOC group.	

3.4 Overview of methodologies of all included studies

Three of the included studies were randomised trials, 2 with a double blind phase followed by an optional open label phase comparing gammaCore and standard care with a sham device and standard care (Silberstein et al. 2016, Goadsby et al. 2018) and one open label trial comparing gammaCore and standard care with standard care alone (Gaul et al. 2016). One study was a post-hoc analysis of a randomised trial (Gaul et al. 2017). An additional 3 non-comparative cohort studies were included, one prospective (Trimboli et al. 2018) and two retrospective (Nesbitt et al. 2015, Marin et al . 2018).

Two trials (Goadsby et al. 2018 and Gaul et al. 2016) were European trials and included UK patients and all 3 of cohort studies were UK based.

Patient numbers ranged from 25 patients in one study (Nesbitt et al. 2015) to 150 patients (Silberstein et al. 2016) with the 3 cohort studies having the lowest numbers of patients. The EAC noted that there is a possibility that there is an overlap between two of the UK based studies (Marin et al 2018 and Nesbitt et al 2015).

Inclusion and exclusion criteria were broadly similar across all studies with the International Classification of Headache Disorders ICHD) definition of cluster headache being used in 6 studies (Silberstein et al. 2016, Goadsby et al. 2018, Gaul et al. 2016, Gaul et al. 2017, Nesbitt et al. 2015 and Marin et al. 2018) and the European Headache Federation definition of refractory cluster headache used in one (Trimboli et al. 2018). The populations in the included studies were not directly relevant to the scope as although they all had cluster headaches, only two of the included studies included exclusively treatment refractory patients as identified in the scope (Marin et al. 2018 and Trimboli et al. 2018) while one study (Nesbitt et al. 2015) reported that 7/19 patients were considered to be treatment refractory. One study (Trimboli et al. 2018) included patients with indications other than cluster headache, in a total study population of 42 patients only 12 had chronic cluster headache and results are reported for these 12 patients only. The EAC did not identify any additional evidence and no additional studies or evidence was highlighted by the clinical experts. Therefore the EAC considers this to be the best available

evidence and considers it unlikely that any large randomised trials would be possible due to the low prevalence of the condition.

The primary outcome was the change in the number of cluster headache attacks experienced by participants however the way in which this was reported was variable across the studies (table 4). One study (Gaul et al. 2016) reported quality of life outcomes and one study (Marin et al. 2018) reported anecdotally on benefits of gammaCore as experienced by participants. None of the included studies reported on the reduction of ECG and blood testing for monitoring of drug treatments or on the use of outpatient and healthcare services, including psychiatric care.

3.5 Overview and critique of the company's critical appraisal

The EAC consider that the company submission used appropriate methods to critically appraise the included studies. The EAC used the Critical Appraisal Skills Programme (CASP) checklists to assess the included studies (appendix D).

Specific methodological issues to consider which were highlighted by the EAC include:

- All results are based on patient reported outcomes which, while appropriate for the outcomes of interest, may be subject to bias
- Subgroup analyses in the randomised trials (Silberstein et al 2016 and Goadsby et al 2018), while informative should be interpreted with caution as the studies were not powered for such analysis
- Only two studies (Marin et al, 2018 and Trimboli 2018) reported specifically restricting to treatment refractory patients.
- Patients were receiving prophylactic treatments at baseline with GammaCore being assessed as acute treatment in two studies (Silberstein et al 2016 and Goadsby et al 2018)
- Although randomised trials are generally considered to provide the best quality evidence, GRADE assessment (Appendix C) suggests that the

certainty of the evidence for the outcomes of interest ranges from moderate to very low. This is as a result of the issues highlighted above.

3.6 Results

Table 4 summarises the results of the included studies by outcome reported.

The EAC note that while each of the included studies reported a response rate to nVNS for cluster headaches, each of the studies measured response either as a reduction in pain intensity or as a reduction in attack frequency depending on whether nVNS was being used acutely or prophylactically.

Overall the published evidence suggests that nVNS as an adjunct to standard care or extra treatment option for treatment refractory patients may have some clinical benefits. The EAC considers that the results should be interpreted with caution as although there were three randomised trials, two of the studies (Silberstein et al 2016, Goadsby et al 2018) conducted subgroup anlaysis investigating outcomes for chronic and episodic headache separately and the studies were not powered for subgroup analysis; in addition, no significant difference was observed between the groups when considering the whole cohort. The third randomised trial was an open label trial in chronic cluster headache patients only.

Two randomised trials, ACT 1 (n=150) and ACT 2 (n=102) reported a increase in patients achieving pain free status;26.7% (nVNS) versus 15.1% (sham), p=0.1 (ACT 1, Silberstein et al. 2016) or in attacks achieving pain free status within 15 minutes of treatment initiation; 14% (nVNS) versus 12% (sham), p=0.71 (ACT 2: Goadsby et al. 2018) when using nVNS to treat cluster headache attacks. The reduction in pain intensity was not significant when considering the whole cluster headache cohort however when looking at patients with episodic cluster headaches only, the reduction in pain intensity was statistically significant in patients using nVNS with standard care compared with those using standard care only.

A third, open label, randomised trial in 97 patients with chronic cluster headache only, the PREVA trial (Gaul et al. 2016) reported a greater

reduction from baseline in mean attack frequency in the nVNS + SoC arm compared with SoC alone with a mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI 0.5-7.2; p=0.02).. Further, post-hoc analysis of the PREVA data including 97 patients (Gaul et al. 2017) suggest that the mean weekly attack frequency was significantly lower with nVNS+SoC compared with SoC alone and results from an conference abstact (Gaul et al. 2018) suggests that average decrease in mean weekly attack frequency was significantly greater for patients using acute nVNS for ≥76.9% of their attacks.

One UK based cohort study (Nesbitt et al. 2015) reported that the addition of nVNS to the patients' standard care suggested a mean improvement in their condition with 15/19 patients reporting improvements from baseline.

Two cohort studies in treatment refractory patients (Marin et al. 2018 and Trimboli et al. 2018) indicated a possible positive effect for patients using nVNS. In a study including 30 patients, mean attack frequency decreased significantly with nVNS (Marin et al. 2018) however in a second cohort study only 1/12 patients showed a ≥30% reduction in weekly CH frequency at month 3 compared with baseline (Trimboli et al. 2018). Trimboli et al (2018) included treatment refractory patients only and appears to be the only study which does not have some involvement from the manufacturer.

Treatment failure (use of rescue medication within first 60 mins of nVNS treatment initiation) did not differ significantly between two groups (Silberstein et al. 2016). A randomised trial (Gaul et al. 2016) reported a decrease in the frequency of abortive medication use in the nVNS arm compared with the comparator arm. Marin et al. (2018) reported that 4 patients were able to use nVNS as monotherapy to manage cluster headache and Nesbitt et al. (2015) reported that 3 patients stopped using oxygen or sumatriptan in favour of nVNS.

One randomised trial (Gaul et al. 2016) assessed quality of life and reported a change in EQ-5D-3L index score above the minimally important difference in the nVNS+SoC group which was considered to be clinically meaningful. One cohort study (Marin et al. 2018) indicated that self reported patient benefits

included decreased interictal headache pain, no longer being housebound, ability to return to work or school, improved sleep, decreased absenteeism, avoidance of surgery intended to treat CH and improved quality of life.

Compliance with treatment plans was formally reported in two studies (Gaul et al, 2016 and Trimboli et al. 2018). Gaul et al reported that 64.4% of patients in the nVNS+SoC arm were ≥80% adherent during the randomised and extension phase and that 50% of participants assigned to the control arm were ≥80% adherent during the extension phase. Trimboli et al reported that only one cluster headache patient was reportedly non-compliant however compliance was measured based on when a patient requested replacement device and is therefore an estimate of compliance. None of the other studies reported any formal method of assessment of treatment compliance.

Table 4: Results from Included Studies

Study	Response Rate – Reduction in pain intensity	Response Rate – Reduction in attack frequency	Pain free at 15 minutes for ≥50% of treated attacks	Rescue Medication Use	Quality of Life
Silbserstein et al. (2016)	Assessed as the proportion of patients achieving a pain intensity score of 0 or 1 at 15 minutes after treatment initiation for first CH attack **All CH:** 26.7% (nVNS) versus 15.1% (sham), p=0.1 **eCH:** 34.2% (nVNS) versus 10.6% (sham), p=0.008 **cCH:** 13.6% (nVNS) versus 23.1% (sham), p=0.48	Not Reported	**All CH:** 11.7% (nVNS) versus 6.9% (sham), p=0.33 **eCH:** 15.8% (nVNS) versus 2.1% (sham), p=0.04 **cCH:** 4.6% (nVNS) versus 15.4% (sham), p=0.36	**All CH:** 38.3% (nVNS) versus 50.7% (sham), p=0.15 **eCH**: 42.1% (nVNS) versus 48.9% (sham), p=0.53 **cCH:** 31.8% (nVNS) versus 53.9 (sham), p=0.13	Not Reported

Study	Response Rate – Reduction in pain intensity	Response Rate – Reduction in attack frequency	Pain free at 15 minutes for ≥50% of treated attacks	Rescue Medication Use	Quality of Life
Goadsby et al. (2018)	Assessed as proportion of all treated attacks achieving pain free status within 15 minutes after treatment initiation. **All CH:** 14% (nVNS) versus 12% (sham), p=0.71 **eCH:** 48% (nVNS) versus 6% (sham), p<0.01 **cCH:** 5% (nVNS) versus 13% (sham), p=0.13 *Odds Ratios (95% CI) from the GEE (adjusted for site in the total cohort and in the cCH subgroup)* **All CH:** 1.22 (0.42-3.51), p=0.71 **eCH:** 9.19 (1.77-47.8), p<0.01 **cCH:** 0.41 (0.13-1.30), p=0.13	Not Reported	**All CH** 17% (nVNS) versus 7% (sham), p=0.15 **eCH** 36% (nVNS) versus 8% (sham), p=0.16 **cCH** 9% (nVNS) versus 7% (sham); p=1.00	Not Reported	Not Reported

Gaul et al. (2016)	Not Reported	Reduction in mean number of CH attacks/week In the ITT population, participants receiving SoC plus nVNS during the randomised phase had a greater reduction from baseline) in the number of CH attacks per week than those receiving control (-5.9 (SE 1.2) versus -2.1 (SE, 1.2)), for a mean therapeutic gain of 3.9 fewer CH attacks per week (95% confidence interval (CI): 0.5, 7.2; p¼0.02) Proportion of patients with ≥50% reduction in mean number of CH attacks per week Response rate was significantly higher in the nVNS+SoC group compared with SoC alone: 40% (18/45) versus 8.3% (4/48); p<0.001)	Not Reported	A 57% decrease in the frequency of abortive medication use was noted in the nVNS+SoC group (Δ= -15 (95% CI: -22.8 to -7.2), p<0.001) compared with (Δ= -2 (95% CI: -9.4 to 5.4), p=0.59) in the control arm (% decrease NR). Changes in abortive medication use were driven by reductions in use of SC sumatriptan (p=0.007) and inhaled oxygen (p=0.02). These reductions were maintained through the extension phase. Addition of nVNS to SoC during the extension phase did not result in a significant reduction in the use of abortive medication (Δ= -3.4, 95% CI: -11.5 to 4.7) p=0.40)	*EQ-5D-3L changes from baseline* In the mITT population (baseline to randomised), changes from baseline were significantly improved for nVNS+SoC compared with SoC alone – (nVNS+SoC minus SoC: Δ=0.194 (95% CI 0.054-0.334), p=0.007) The change in EQ-5D-3L index score in the nVNS+SoC group was above the MID (0.074) and considered clinically meaningful. Addition of nVNS to the control group (extension phase) was associated with a clinically meaningful change (0.078 points (95% CI -0.02 to 0.18) In the randomised phase, change from

Study	Response Rate – Reduction in pain intensity	Response Rate – Reduction in attack frequency	Pain free at 15 minutes for ≥50% of treated attacks	Rescue Medication Use	Quality of Life
					baseline VAS score was greater for nVNS+SoC (nVNS+SoC minus SoC: ∆=8.93 points (95% CI 0.47-17.39, p=0.039) Changes in mean HIT scores were greater in the nVNS+SoC group compared with SoC alone and were above the MID (-2.3 points), the absolute mean HIT scores suggest CH attacks have a substantial impact on QoL (data NR)

Study	Response Rate – Reduction in pain intensity	Response Rate – Reduction in attack frequency	Pain free at 15 minutes for ≥50% of treated attacks	Rescue Medication Use	Quality of Life
Gaul et al. (2017)	Not Reported	A significantly higher proportion of patients in the nVNS+SoC group had attack frequency reductions from baseline (≥25% and ≥50% reduction, p<0.001; ≥75% reduction, p<0.009). 3 patients (8%) in the nVNS+SoC group had a 100% attack frequency reduction versus 0% in the SoC group.	Not Reported	Not Reported	Not Reported
Nesbitt et al. (2015)	Not Reported	There was a reported reduction in 24 hour attack frequency with prophylactic nVNS from a mean 4.5 to 2.6.	Not Reported	3 patients stopped using oxygen (n=2) or sumatriptan (n=1) in favour of nVNS. N=10 patients reduced oxygen use by an estimate mean of 55%±8%; 3 continued to use the same amount of oxygen and 1 patient reported an increase by 100% N=3 patients were able to stop using triptans but continued to use some oxygen and 9 patients reduced their use of triptans by a mean of 48%±6%.	Not Reported

Marin et al. (2018)	Not Reported	Mean (range) attack frequency with SoC was 26.6 (3.8-77.0) attacks/week. This decreased to 9.6 (0-38.5) attacks/wk with SoC+VNS (p<0.01)	Not Reported	Patients used a mean (range) of 0.8 (0-2) preventative treatments before initiation of nVNS versus 0.7 (0-2) after nVNS initiation. Mean (range) number of acute treatments used was 1.8 (1-4) before nVNS initiation versus 1.1 (0-2) after. N=22 patients used triptan injection or nasal spray as acute treatment before nVNS initiation; 9 (41%) stopped and 12 (55%) decreased their triptan use during nVNS treatment N=27 (93%) patients reported using high-flow oxygen as acute treatment prior to nVNS initiation; 9 (33%) stopped and 17 (63%) decreased their use Overall, N= 3 patients were able to manage their condition with preventative pharmacological treatment only and N=4 were able to use nVNS as monotherapy	Benefits reported by patients during evaluation included: • Decreased interictal headache pain • No longer being housebound • Ability to return to work or school • Improved sleep • Decreased absenteeism • Avoidance of surgery intended to treat CH • Improved quality of life

Study	Response Rate – Reduction in pain intensity	Response Rate – Reduction in attack frequency	Pain free at 15 minutes for ≥50% of treated attacks	Rescue Medication Use	Quality of Life
Trimboli et al. (2018)	Not Reported	Assessed as ≥30% reduction in headache days after 3 month treatment N=1 showed ≥30% reduction in weekly CH frequency at month 3 compared with baseline. This patient also reported a reduction in oxygen use. N=2 reported a slight improvement from baseline N=3 reported no change N=6 reported a worsening in weekly frequency *Abortive Effect* N=0 reported headache relief using nVNS	Not Reported	Not Reported	Not Reported

3.7 Description of the adverse events

Adverse events reported in each study are summarised in table 5. The EAC noted that the cohort studies (Nesbitt et al. 2015, Marin et al. 2018, and Tromboli et al. 2018) did not clearly differentiate between device related adverse events and non-device related attack simply reporting all as adverse events. One study (Gaul et al. 2018) did not report any adverse events however the EAC acknowledge that this was because the adverse events for the study cohort had been reported in a previous publication (Gaul et al. 2015).

Reported adverse events were mild to moderate in all studies with no participants discontinuing nVNS due to adverse events. The most common adverse events related to device use were localised skin tingling or irritation, burning, muscle soreness and/or redness at application site.

The EAC noted that the company submission included studies using GammaCore for indications other than cluster headache in reporting adverse events. The EAC acknowledges that device related adverse events may be similar for all indications however it is not clear whether different indications require different nVNS treatment protocols which may have an impact. It is less clear whether non device related adverse events would be similar for all indications and again whether these might be impacted by differences in treatment protocol.

The EAC considers there is sufficient evidence that there are no serious device related adverse events in the cluster headache population, which is the scope population and that the additional studies are not needed.

The EAC did not identify any additional adverse events compared to the company's submission when searching the MHRA or MAUDE databases.

Comments from clinical experts suggest that gammaCore is safe and easy to use for patients with cluster headache. Two clinical experts described gammaCore as easy to use and patient and user friendly. Two clinical experts suggested that there were very few side effects and one clinical expert suggested that there was no need for safety monitoring.

Table 5: Adverse Events

Study	**Serious Adverse Device Events**	**Adverse Device Events (Any)**	**Application Site Reactions: Burning, tingling, soreness, stinging, skin irritation, redness, erythema**	**Musculoskeletal Reactions: Lip or facial drooping, pulling, twitching**	**Nervous System Disorders: CH Attack, Dizziness, Headache, Dysgeusia, metallic taste**	**Serious Adverse Events**	**Adverse Events**	**Treatment Discontinuations**
Silberstein et al. 2016 Double Blind Phase Only	None	N=35 reported ≥1 ADE nVNS+SoC N=11 SoC N=24	nVNS+SoC N=2 SoC N=16	nVNS+SoC N=8	SoC N=7	nVNS + SoC N=1 Cluster Headache	N=49 reported ≥AE nVNS + SoC N=18 Sham+SoC N=31	None Reported
Goadsby et al. 2018 Double Blind Phase Only	None	N=19 reported ≥1 ADE nVNS+SoC N=9 Sham+SoC N=10	nVNS+SoC N=7 Sham+SoC N=3	nVNS+SoC N=1	None	nVNS+ SOC N =1 (severe lower abdominal and back pain)	N=34 reported ≥1 AE nVNS+SoC N=20 Sham+SoC N=14	None Reported

Study	Serious Adverse Device Events	Adverse Device Events (Any)	Application Site Reactions: Burning, tingling, soreness, stinging, skin irritation, redness, erythema	Musculoskeletal Reactions: Lip or facial drooping, pulling, twitching	Nervous System Disorders: CH Attack, Dizziness, Headache, Dysgeusia, metallic taste	Serious Adverse Events	Adverse Events	Treatment Discontinuations
						Sham+SoC N=1 (severe depression and anxiety)		
Gaul et al. 2016 Safety Population	None	N=20 reported ≥1 device related AE nVNS+SoC N=13 SoC N=7	None	nVNS+SoC N=3	nVNS+SoC N=8 SoC N=9	nVNS+SoC N=2 SoC N=2	N=49 reported ≥1 AE	None reported
Gaul 2017	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016	Reported in Gaul 2016
Nesbitt et al. 2015	None	None	None	None	None	None	N=2 patients reported side	None Reported

Study	Serious Adverse Device Events	Adverse Device Events (Any)	Application Site Reactions: Burning, tingling, soreness, stinging, skin irritation, redness, erythema	Musculoskeletal Reactions: Lip or facial drooping, pulling, twitching	Nervous System Disorders: CH Attack, Dizziness, Headache, Dysgeusia, metallic taste	Serious Adverse Events	Adverse Events	Treatment Discontinuations
							shifting of attacks N=1 patient reported transient worsening of pain	
Marin et al. 2018	None	None	Observed but numbers not reported	None	None	None	None	None Reported
Trimboli et al. 2018	None	N=5	N=2 temporary hoarseness/sore throat N=1 swollen/red skin around the face and	N=1 facial twitching	None	None	None	None

Study	Serious Adverse Device Events	Adverse Device Events (Any)	Application Site Reactions: Burning, tingling, soreness, stinging, skin irritation, redness, erythema	Musculoskeletal Reactions: Lip or facial drooping, pulling, twitching	Nervous System Disorders: CH Attack, Dizziness, Headache, Dysgeusia, metallic taste	Serious Adverse Events	Adverse Events	Treatment Discontinuations
			neck N=1 nausea (resolved by not using nVNS immediately after meals) N=1 increased frequency of bowel movements/flatus in one patient					

3.8 Description and critique of evidence synthesis and meta-analysis

The company submission included results of a pooled analyis of the ACT1 (Silberstein et al. 2016) and ACT2 (Goadsby et al. 2018) trials (deCoo 2019). The results from the pooled analysis suggest that a statistically significant proportion patients with episodic cluster headache achieve responder status at 15 mins (pain score 0-1) for their first attack when using nVNS compared with standard care and a statistically significant proportion of episodic cluster headache attacks achieve pain free status at 15 minutes. The proportion of patients with responder status for ≥50% of attacks was statistically significantly greater for nVNS versus standard care in the episodic subgroup.

The EAC noted some key issues to be considered when interpreting the results of the pooled analysis.

The company submission included a critical appraisal of the pooled analysis however it used the same appraisal as for randomised trials which the EAC does not consider appropriate. The EAC noted however that there is no 2019 deCoo publication only a conference abstract published in 2017. As this is a conference abstract it cannot be critically appraised by the EAC using an appropriate checklist due to a lack of information. In particular, details of the methodology of the pooled analysis is limited both in the conference abstract and in the company submission.

The data extraction table for deCoo 2019 includes outcome data which is not reported in the ACT1 (Silberstein et al. 2016) or ACT2 (Goadsby et al. 2018) publications and so cannot be verified by the EAC although the company have confirmed that this is data collected during the trials. Details in the methods section suggests that the data for the two trials were simply pooled and analysed as a single dataset with no weighting given to the contribution of each of the individual trials. The methods section of the extraction table states that a fixed effects meta-analysis was used to estimate the pooled effects as the ACT 1 and ACT 2 studies were homogenous for participants and results however no data has been presented to support this. The EAC also noted that

the company submission stated ‘no formal statistical tests for heterogeneity were performed’ and considers this to an important omission.

One rationale for pooling the data given by the company was the need for greater statistical power to evaluate differential effects among episodic and chronic cluster headaches The EAC agrees with the company submission which notes that the studies were not individually powered to investigate episodic and chronic cluster headache subgroups, however the EAC does not agree that pooling the data and analysing it as a single dataset provides statistical power, no power calculations for subgroup analysis have been presented in either of the individual studies therefore there is no indication of what sample size would be appropriate. The main principle of meta-analysis is that the summary results of the separate trials are combined not the individual data (Deeks et al 2011). Without the use of formal meta-analysis methods which include individual study weighting and heterogeneity assessments, it is possible that results may be inaccurate and misleading.

Overall, based on the information in the data extraction table for deCoo 2019, the EAC considers this pooled analysis to be a post-hoc simple pooled analysis of trial data rather than a formal meta-analysis and suggests the results be viewed with caution. The EAC does not consider there to be a benefit to conducting a pooled analysis of the data due to the methodological limitations of such an analysis. The EAC also considers that as the randomised trials do not represent a treatment refractory population and gammaCore is being investigated as acute treatment only therefore a more formal meta-analysis will add limited information at this time however should the clinical pathway be redefined to include the whole cluster headache population there may be some benefit to investigating whether it would be possible to conduct a meta-analysis of all three randomised trials provided the appropriate outcome data have been collected and could be made available.

Addendum June 2019

Following submission of the Assessment Report, the full publication became available online (deCoo, 2019).

Results from the pooled analysis suggest a significant increase in the proportion of episodic cluster headache attacks that achieve a treatment response at 15 minutes with nVNS (GammaCore) compared with a Sham device (39% versus 12%; Absolute Difference 27%, OR=4.67 (1.77-12.32), p=0.01). This result appears to be driven by the data from the ACT1 trial which had a much higher proportion of patients with episodic cluster headache compared with the ACT2 trial (n=101 in ACT1 and n=30 in ACT2). The pooled results also suggest a significant increase in the proportion of episodic cluster headache attacks that are pain free at 15 minutes with GammaCore compared with a Sham device (24% versus 7%, Absolute Difference 17%, p<0.01). The EAC note that there is a discrepancy between text and tables with the text reporting an absolute difference of 22%. Full results from the pooled analysis are detailed in Appendix B.

The EAC have reviewed the full publication and consider that the issues highlighted in Section 3.8 remain pertinent and should be considered when interpreting the results of the analysis. Critical appraisal of the full publication using the AMSTAR checklist (Shea et al, 2017) suggests that the review is of very low quality (Appendix D).

Key points to consider include:

- this is a post-hoc simple pooled analysis of trial data not a meta-analysis
- no heterogeneity assessment or weighting values for the individual studies have been detailed
- pooling the data and analysing it as a single dataset does not mean the study is powered for subgroup analysis.
- no power calculations for subgroup analysis have been presented in either of the individual studies therefore there is no indication of what sample size would be appropriate

3.9 Ongoing studies

The EAC did not identify any ongoing studies to add to the report.

4 Economic evidence

Published economic evidence

4.1 Critique of the company's search strategy

The company submission included a systematic literature search of key databases relevant to economic publications. The EAC conducted a search for economic evidence and did not identify any additional studies for inclusion. The EAC did note one minor discrepancy in the reporting of search results suggesting that a total of 143 papers were identified and 36 duplicates removed (section 8.1.2) however section 8.1.3 states 133 abstracts were identified after removal of duplicates. The EAC considers 133 to be the correct value as this is number stated in the PRISMA diagram.

4.2 Critique of the company's study selection

Details of the inclusion and exclusion criteria in the company submission are presented in table 1 along with EAC observations and comments.

4.3 Included and excluded studies.

The company submission identified three cost utility models with a payer perspective, two of which were for gammaCore and one for sphenopalatine ganglion (SPG) stimulation. All were in chronic cluster headache patients and all compared costs with acute use of standard of care which comprised triptans and/or oxygen.

The PRISMA diagram stated that the cost utility models were reported in a total of seven publications but includes data extraction tables and quality assessments for only three publications (Morris 2016, Mwamburi 2017 and Pietzsch 2015). Based on searches carried out, the EAC agrees that the 3 publications included in the company submission represent key economic publications. The additional 4 studies were not referenced in the submission. Three were identified by the EAC as abstracts by Gaul at al. (2015a,b,c) which contain no additional information, and Pietzsch et al. (2017) which relates to medication reduction following implantation of an SPG device.

The company excluded all of these studies as direct evidence for the economic submission, however they did describe the studies, as context and

validation for the de novo model. The EAC did not consider any studies to have been excluded inappropriately and agree that a brief discussion of previous models is useful for understanding the submitted model, although the overall findings are not directly applicable to the UK context.

The EAC also identified two additional models for cost-effectiveness of gammaCore, although in a slightly different population (Mwamburi et al. 2018, Jenks et al. (2016a,b). Again, the overall findings have limited applicability, however the studies are useful for comparing structure and inputs to the models.

Mwamburi et al (2018) report cost-effectiveness of gammaCore for acute treatment of episodic migraine from a USA perspective. While a conference abstract (Jenks 2016a) and a poster (Jenks 2016b) describe a cost utility model based in the UK. These do not have sufficient information for a full critique, but point to some variation in approach and assumptions. The evidence may not be directly applicable to the population specified in the scope, however it provides a valuable context to understanding the de novo model structure and validity. For this reason the EAC have included a summary in the following section.

4.4 Overview of economic studies

All studies discussed in this section have been excluded as not being directly applicable to the scope, but are useful as validation and context to the submitted model. They are summarized in table 6. All of the identified models for gammaCore include a company employee as a co-author.

The most relevant gammaCore study comprises a Markov Chain Monte Carlo simulation in chronic cluster headache patients from a German payer perspective with the publication also reporting outcomes for the UK although this was not the main purpose of the model and the results are presented briefly as part of the discussion (Morris et al 2016). This model is subsequently used as the basis for the submitted de novo model. No details were published of the inputs or structure of how the model was adapted to a UK perspective.

Morris et al (2016) base the resource use on clinical data from the PREVA study (Gaul et al, 2016) with costs for acute medication for headache attacks. They report gammaCore to be dominant compared to standard care, from a German perspective (cost saving and cost effective), however the UK perspective reported is cost-effective, but with a cost incurred for gammaCore compared to standard care. EAC communications with the author confirmed that the only changes made to adapt to a UK perspective were to map utilities to UK preferences and to use UK based costs.

Both Morris et al (2016) and Mwamburi et al (2017) are Markov models based on responder and non-responder states. Mwamburi et al. (2017) differentiates non-responder into partial responder (below the threshold, but still gaining some benefit) and “failure” where no benefit is received. Mwamburi et al (2017) also include re-training costs, with some patients then moving into the responder state.

Mwamburi (2017) calculate an annual cost for treating cluster headaches (based on Polson 2017) and apply a cost reduction factor to all patients in the responder state. This is stated as being based on ACT1, ACT2 and Strickland (2018), an NHS cohort study into patients with primary headache and multi-morbidity. The model appears to be driven by the size of the cost-reduction factor, but no more details are given as to how this was calculated. Mwamburi et al. (2018) use a similar approach, but with data for the migraine population.

Both models reported by Mwamburi et al (2017,2018) found gammaCore to be dominant when compared to standard care in the US.

Pietzsch et al. (2015) looked at a different technology, but also split patients into responders and non-responders. The model compared Sphenopalatine ganglion stimulation (SPG), an implantable nerve stimulation system, with standard care. Costs were based on the cost of the implantable technology, together with the procedure and complications, and the reduced use of medication for acute attacks. The full paper from a German perspective found SPG to be cost incurring compared to standard care, but cost-effective. An Pietzsch et al. (2017) reported reduced medication use in the UK following

SPG implantation. These have limited relevance due to the very different cost implications for implantable devices.

A poster and abstract by Jenks et al. (2016a, 2016b) were based on an NHS cohort study reported in Strickland et al. (2016) and in a full paper at a later date (Strickland et al. 2018). The included cohort were patients with primary headache and multi-morbidity. The costs were based on the number of GP consultations, secondary care visits and the overall number of prescriptions. Jenks et al (2016a, 2016b) found gammaCore to be cost effective compared to standard care, but cost incurring, in this UK based study for primary headache. There was no mention of the costs for abortive medication for acute attacks, and the prescriptions were costed at a general figure of £8.25 each.

An additional ten cost analyses were included in the manufacturer submission. These look at general costs for cluster headaches, or reductions in medication use. The different technologies, and different healthcare systems for these studies mean that there is very little relevant information available. They do not include modelling, but are rather a description of specific costs. The EAC support the exclusion of these studies, however a brief summary of their population and setting is included in Appendix F

Costs included in other models that are not considered in the Morris et al (2016) model, or the submitted model, include GP and hospital consultations (for any reason), prescriptions (for any reason), initial visits to nurse to discuss possibility of using gammaCore, any repeat training of patients to improve response rates, and scheduled review consultations. The relevance of these to the submitted model and their potential impact will be discussed in the following sections.

Table 6: Summary of economic models (none directly relevant to scope)

Study	Setting	Technology	Population	Study data	Key differences	outcomes
Morris 2016	Germany	gammaCore (prophylactic)	Chronic CH	PREVA	Monthly cost, no free period Medication taken from mean values across whole arm.	Dominant
Morris 2016[$]	UK	gammaCore (prophylactic)	Chronic CH	PREVA	Changed utility mapping and costs to UK values, these not specified	Cost incurring, cost effective
Mwamburi 2017	USA	gammaCore (acute)	Episodic CH	ACT1, ACT2	Non-responders receive additional training and some then become responders.. Apply a cost reduction factor to all treatment costs if gammaCore effective. Three states: responder, partial responder and failure (0% response)	Dominant
Mwamburi 2018	USA	gammaCore (acute)	Episodic migrane	PRESTO + Strickland 2018		Dominant
Pietzsch 2015	Germany	sphenopalatine ganglion (SPG)	Chronic CH	Pathway CH1	Cost of device, implantation procedure and associated complications	Cost incurring, cost effective
Pietzsch 2017[#]	UK	SPG	Chronic CH	Pathway CH1	Reports reduced cost of medication but does not appear to model full pathway	Reduced cost of medication
Jenks 2016[#]	UK	gammaCore (prophylactic)	Primary headache with multi-morbidity.	Strickland 2018 (NHS cohort study)	Based on reduced primary and secondary care plus slight increase in overall prescriptions with gammaCore. No triptan costs specified, generic prescriptions only. Includes review appointments. Bi-monthly cost of gammaCore. 1.8 nurse visits per patient that then outpatients for gammaCore.	Cost incurring, cost effective
Thavanes waran 2016[#]	UK	Occipital Nerve stimulation	Medication refractory Chronic CH	Literature review	Main drivers stated as hospitalisation and acute medication, but results based on medication use only.	Cost saving

[$] brief mention in Morris (2016), no separate publication
[#] abstract and/or poster

4.5 Overview and critique of the company's critical appraisal for each study

The company submission included quality assessment checklists for each of the three full text cost effectiveness publications. The checklist was based on criteria recognized by the York Centre for Reviews and Dissemination (CRD, 2008). The EAC agrees that this was an appropriate approach to critical appraisal and agrees with company assessment that the three cost evaluations represent high quality evidence, for the technologies and perspectives that they model. None of the papers are directly applicable to the current submission.

Does the company's review of economic evidence draw conclusions from the data available?

The company submission includes a de novo cost analysis and therefore does not draw any conclusions on the cost effectiveness of the published data in isolation. The company submission compares the results from one published economic analysis (Morris 2016) highlighting a number of reasons why results of the de novo cost analysis differ from the published evidence.

The submission correctly states that all models found gammaCore to be cost-effective, and that the UK adaptation of the German model found an ICER of £166.12/QALY gained. Although cost savings were found in German and USA settings, the UK adaptation found gammaCore to be cost incurring.

4.6 Company de novo cost analysis

Patients

The model is for patients with chronic cluster headaches (cCH). It does not include patients with episodic CH. Patients in each arm are split into responders and non-responders, with responders defined as having at least a 50% reduction in the number of attacks in the given time period.

The submission bases the exclusion of eCH on a lack of available data and the probability that UK patients with eCH would not be expected to receive gammaCore. This is based on the Marin et al. (2018) study where only 1 out

of 30 (3%) patients with cluster headaches had eCH. However, Nesbitt et al. (2015) included 8 out of 19 (42%) patients with eCH. Trimboli et al. (2018) included 12 patients with cluster headache, none with eCH, however the study was for primary chronic headache. One expert comment was that approximately 20% of their patients with cluster headache would have eCH.

The PREVA study does not include patients with eCH, however ACT1 and ACT2 do, and have been used to model the cost-effectiveness of gammaCore as acute treatment for episodic cluster headaches (Mwamburi et al. 2017). ACT1 and ACT2 did not consider preventative use of gammaCore.

Technology

The technology modelled is gammaCore in addition to standard care. The model is based on the PREVA trial which specified 3 doses twice a day (in total 6 doses a day) for prophylactic use, with patients also able to take additional doses as acute treatment for attacks.

Comparator(s)

Standard care is modelled as abortive medication use only, and limited to use of oxygen, zolmitriptan and sumatriptan. It is assumed that prophylactic medication would be the same in both arms of the model and is therefore not included.

The company have excluded verapamil (preventative) as a separate comparator, based on the limited data available. It is used as part of standard care in the PREVA trial, however patients were not permitted to change their prophylactic medication. It is likely that gammaCore would be adjunctive to use of verapamil where this formed part of existing standard care for patients.

Sphenopalatine ganglion nerve stimulators (SPG) were not included as comparators, and the EAC agree that gammaCore is likely to be introduced before more invasive options. The company also note that current NICE IP guidance for SPG is that it should be used with special arrangements only

(NICE IPG527). The EAC note that this is currently also the case for gammaCore (NICE IPG552).

Occipital nerve block is also not included as a comparator, and the company state it is unlikely to be used in the UK. It is not included in options in NICE pathways or NHS Choices, however a number of trusts do have leaflets available, and one expert said that is was widely used as a rescue treatment for short term benefit.

Model structure

The model is from an NHS and personal services perspective, over a 1 year time horizon. There is no discounting included which is appropriate for the modelled time length. The model is based on data from a 4 week period, with an additional 4 week extension, and therefore restricting the time horizon to 1 year is reasonable.

The structure is a Markov Model with a 1 month cycle, which is an appropriate length. The states in the model are 'responder' and 'non-responder' with responder being defined as having at least a 50% reduction in the number of attacks during the assessment period. In the submitted base case there are no changes in the proportion of responders or non-responders after the first month. Following on from this, there are only very limited variation in resource use or cost from one month to the next.

Figure 1 taken from Figure C1:of the company submission

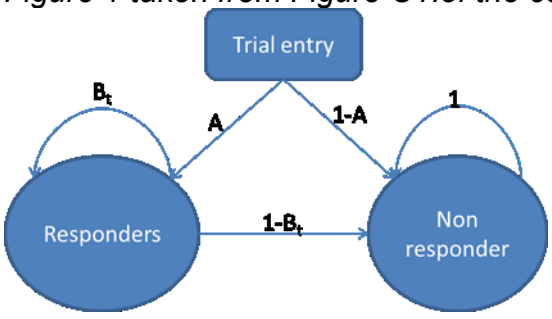


Table 7 shows the proportion of patients in each state of the model in the 1st and subsequent months. All costs are either direct costs of gammaCore prescriptions, or costs for acute medication use. Medications costs are taken

from post-hoc analysis of the PREVA trial, and the patient groups used for the analysis in each state are also shown in table 7.

Table 7. Base case: movement of patients between states, and resource use used throughout model.

	gammaCore		Standard care	
	Responder	**Non-responder**	**Responder**	**Non-responder**
Percentage of patients in each state				
1st month	40%	60%	8%	92%
2nd, 3rd and subsequent months	27.6%	72.4%	0%	100%
Resource use group for patients in each group and arm				
1st - 3rd months	gammaCore responder	gammaCore non-responder on treatment	SOC responder (=gammaCore responder)	SOC non-responder
Subsequent months	gammaCore responder	SOC non-responder	SOC non-responder	SOC non-responder
Total monthly cost for patients in each arm				
1st month	£169		£308	
2nd, 3rd months	£182		£326	
Subsequent months	£324		£326	

These values are for the base case only, as submitted scenarios have different values for:

- Initial proportion responding to gammaCore
- Rate at which initially responding patients discontinue using gammaCore
- Resource use for gammaCore non-responder group.

Key assumptions

Table 8: Key assumptions

Assumptions identified by company	EAC comment
In the base case, treatment response is defined as ≥50% reduction from baseline in the number of CH attacks per week.	This is a reasonable assumption, and scenario analysis investigates the impact.
Response rates to gammaCore in PREVA are generalisable to those of patients eligible for gammaCore in the NHS	PREVA sites were split across Europe, with 24 out of 97 patients treated in the UK. All patients have chronic cluster headaches, but there is no explicit criteria that they are refractory to medication. The expectation is that patients in the UK would be refractory to medication.
Beyond 1 month, responders in the SoC group are assumed to be non-responders.	There no explanation given for this assumption. If this were not true, the cost saving would be reduced to £251.08. However, medication use for SOC responders in the first month is based on that used by gammaCore responders which is expected to be a conservative assumption. Subsequently it is based on the mean value for the whole SOC arm,.
Non-responders in the gammaCore plus SoC group are assumed to discontinue prophylactic treatment with gammaCore after the 3-month evaluation period but continue use of abortive treatments.	Non-responders may still receive a reduction in the number of attacks up to 50%. It is possible that some of this group would want to continue using gammaCore. Submitted scenarios have an option for defining “response” as only a 25% reduction in treatment.
Patients are reassessed every 3 months for ongoing response and non-responders in the gammaCore plus SoC group discontinue prophylactic treatment with gammaCore.	The model does have options to work in this way, but the base case has no change in the proportion of responders and non-responders after the initial month. It is included in sensitivity analysis.
Discontinuation occurs in 3-month blocks in line with prescriptions for a gammaCore refill.	This is the model submitted by the manufacturer, other time periods have been used historically. In the base case there is no discontinuation except after the initial trial. It is considered in sensitivity analysis.
Use of abortive medication conditional on responder status is assumed to remain constant	gammaCore non-responders in 1st 3 months are assumed to use a reduced amount due to receiving some benefit from gammaCore. Medication use is taken from a 2 week period, and the total follow-up period was only 8 weeks.
Additional assumptions identified by EAC	
gammaCore costs are not included in the sensitivity analysis.	Although this is set by the company and therefore currently known, there is evidence of it varying

	between settings and over time. Inclusion in the EAC sensitivity analysis demonstrates the impact of this. Additionally the number of free months and the duration of a prescription could be varied (Jenks et al. 2016)
No adverse events are included	This is supported by the clinical evidence. If medication use is reduced, then this is likely to be a conservative assumption.
No changes in number of appointments, in or outpatient or GP	If gammaCore is effective, this would be conservative assumption. This is backed up by UK figures reported in Jenks 2016, although for a slightly different population.
No cost for initial consultation, training or support to patient.	This is likely to only be a small increase in gammaCore costs. Experts have advised that no significant changes to the pathway are required to implement gammaCore. EAC scenarios have investigated the potential impact.
It is valid to use post-hoc analysis of patients into responder / non-responder groups to calculate resource use.	There is a possibility of introducing bias by additional post-hoc analysis of data. Not all patients are included (as not all had resource data), and the number of included patients in the post-hoc analysis and Gaul at al.(2016) differ.

Summary of the base case

Table 9: Company's base case results for 1st year of use (including free trial period). Positive values are cost saving, negative values are cost incurring.

	gammaCore plus standard care	**Standard care**	**Cost saving per patient**
gammaCore	*£517.18*		*-£517.18*
Sumatriptan	*£2,577.39*	*£3,505.53*	*£928.13*
Zolmitriptan	*£206.33*	*£204.85*	*-£1.48*
Oxygen	*£147.55*	*£188.49*	*£40.95*
Total	*£3,448.45*	*£3,898.86*	*£450.42*

	Base-case	**Lowest estimate**	**Highest estimate**
Range of cost-savings with gammaCore	£450.42	-£103	£1,120

These are taken from the lowest and highest cost savings reported in the submitted one-way sensitivity analysis. The lowest estimate is £103 cost incurring.

Clinical parameters and variables

The clinical parameters used are the percentage of patients who are classed as responders and non-responders based on at least a 50% reduction in frequency of attacks. All these parameters are based on the PREVA trial. A small number are drawn directly from the main published paper (Gaul et al. 2016) reporting the study. The majority of parameters are from post-hoc analysis. Some of these results are reported in Morris (2016), the majority are unreported elsewhere. It is reasonable to use clinical outcomes from study data, however where it is unreported elsewhere the EAC is unable to check the values or critique the appropriateness of the values selected to report or the methodology

The PREVA trial is for patients with chronic cluster headaches, using gammaCore as a prophylactic with 2 treatments of 3 doses each day. However there are no inclusion criteria that require the patients in PREVA to be refractory to treatment, although the authors do suggest in the discussion that patients in PREVA are refractory to medication. The EAC asked the company for further details, and the full inclusion criteria are included in Appendix H. These do not include any requirements to have tried alternative medication without success. Trimboli et al (2018) suggest that the response in refractory patients may differ from patients who are not.

The model is intended to be for patients who are refractory to other medication. The only study that clearly defines criteria for medication refractory patients, and has this as an inclusion criteria is Trimboli et al. 2018 This study finds that only one out of 12 patients with chronic CH had a reduction >30% in weekly CH frequency. Three patients were offered continued use of gammaCore. One patient elected to continue using gammaCore at the end of the 3 month long study, and discontinued after 10 months. There was no reduction in sumatriptan use Both the studies reported by Marin et al. (2018) and Nesbitt et al. (2015) included some patients who were described as medication refractory. In both these studies there was a decrease in frequency of attacks and a decrease in the use of abortive medication. Further details of the studies are in section 3.3.

Resource identification, measurement and valuation

Resource use is based entirely on the direct cost of providing gammaCore and the included abortive medications as recorded in the last 14 days of the PREVA trial. PREVA is spread over a number of European sites with the 24 of the 97 patients treated in the UK, 13 of whom were in the gammaCore arm. The study had a 4 week run-in phase followed by a 4 week randomised phase and a further 4 weeks extension where patients receiving standard care were able to receive gammaCore.

The company stated in EAC communications that the resource use data for the gammaCore arm is taken from 35 patients in the PREVA trial who had

“matched data (attack frequency and resource use) available from both the randomised phase and the open label phase of the PREVA study. 35 is the validated number and all of the data for the model was produced and validated by an independent statistician”.

17 of the 35 were responders (at >50%), and the resource use for these 17 patients is used for the gammaCore responder arm. The 35 patients are drawn from a total of 45 ITT randomised to gammaCore plus standard care. The inadequate handling of missing data by using complete case analysis introduces potential bias.

Gaul et al. (2016) report data on sumatriptan and oxygen use for 32 patients who are reported as having information available at baseline and the end of the randomised phase. The company were asked about the difference in numbers, and explained that they were unable to match exactly the same patients that were used in the original analysis. The full response is included in the EAC correspondence log.

The Standard care data is taken from a set of 42 patients from a total of 48 ITT in the randomized phase. This is used for both the standard care arm, and all but the first 3 months of the gammaCore non-responder.

Table 10: Base Case Resource Use

	mean	SD	Standard Error
gammaCore responders (50% reduction) n = 17			
zolmitriptan	**0.6**	*1.54*	*0.37*
sumatriptan	**2.5**	*3.78*	*0.92*
oxygen	**2.2**	*4.71*	*1.14*
Standard care, n = 42			
zolmitriptan	**1.3**	*3.6*	*0.56*
sumatriptan	**7.5**	*9.6*	*1.48*
oxygen	**10.8**	*15.3*	*2.36*
gammaCore non-responders, used for first 3 months only , (50% reduction) n= *18*			
zolmitriptan	**2.5**	7.4	1.74
sumatriptan	**4.1**	9.23	2.18
oxygen	11.2	14.77	3.48

PREVA resource use is reported in Gaul et al (2016) by treatment group at baseline, the last 14 days of the randomized phase and the extension phase. The figures in Gaul et al (2016) show that for both subcutaneous sumatripton and oxygen, there is an increase in medication use between the randomized and extension phase. This may be driven by individual patients increasing their medication use over time, or it may be driven by the inclusion of cross-over patients. These patients were reported as having no significant changes following commencement of gammaCore. Gaul et al (2016) speculate that this may be because of improvements in their condition due to placebo effect in the randomized part of the trial may mask any impact due to gammaCore. This assumes that the placebo effect of being in a trial is greater that the placebo effect of believing that you are being given a new effective treatment. It is also possible that the effect seen by the gammaCore arm during the randomised element was exaggerated by the placebo effect.

Marin et al (2018) and Nesbitt et al (2015) are both UK studies including treatment refractory patients. Both of these found a reduction in the number of attacks and a reduction in the use of triptans. Trimboli et al. (2018) is also a UK study including only patients who are treatment refractory finding that for 12 patients with cluster headaches, only 1 had >30% reduction in attack frequency. None of these UK studies are comparative, and patient numbers are small. The studies are discussed in more detail in the clinical evidence.

The proportion of patients taking nasal vs. subcutaneous sumatriptan was taken from unpublished patient-level data from Marin et al. (2018). One expert advisor felt that this reflected their experience.

There are no resource uses modelled for inpatient, outpatient or GP resources associated with attacks. If gammaCore is effective then this would be expected to be a conservative assumption, since gammaCore would reduce the frequency of attacks, and therefore the frequency of associated resources.

There are no resource uses modelled for any psychological support required to cope with the results of chronic unresponsive cluster headaches. Again this would be expected to be a conservative assumption since gammaCore is modelled as improving outcomes (shown as reduction in medication use).

There are no costs or resources included for adverse events, although the submission states that adverse events directly associated with gammaCore are very rare.

Any adverse events associated with cCH are also not modelled.

Technology and comparators' costs

GammaCore is provided at no cost for the initial 3 months trial. After this there is a requirement to purchase a card every 3 months to allow the device to function. The refill card activates the gammaCore device so that it is able to deliver 93 consecutive days of nVNS therapy. On each of the 93 days, a patient can use a maximum of 30 stimulations within that 24 hour period. After 24 hours, another 30 doses will become available. The gel is replaced along with the refill card. There is no additional cost, and if patients require extra gel for any reason, the company will send this free of charge. Training is provided free of charge by electroCore. There are no other costs to gammaCore included in the model.

This charging model can vary between different countries and at different time points. Other previous models have been costed on the total number of doses

(Morris 2016), or refills may be every one or two months (Jenks 2016). Not all models include an initial free trial, and the duration of this may vary.

In addition Jenks et al (poster) included the cost of a nurse led discussion of gammaCore with patients prior to deciding on treatment. The cost was based on 1.9 appointments at £11.37 each for every patient who actually entered the model.

Sensitivity analysis

Costs of the technology are not included either in the one way or probabilistic sensitivity analysis. Although current prices may be known with certainty this does not allow us to consider the impact of negotiation of different pricing structures, or future changes in costs.

There is no consideration of changing the charging model, for instance to have a different trial length at the start of use, or to prescribe in 1 month or 3 month periods.

The probabilistic sensitivity analysis also excludes gammaCore costs.

The submission included extensive scenario analysis, each using resource data from unpublished post-hoc analysis of the PREVA trial. The resources were calculated on subgroups depending on the response rate seen.

Number of patients in the gammaCore responder sub-groups varied between 10 and 26 patients. The mean use of sumatriptan in the gammaCore responders varies between 2-3 doses per 14 days.

It should be noted that use of sumatriptan remains relatively constant between the subgroups, and that as this is the main driver of costs, there is little change in the results.

Table 11: Scenario Resource Use PREVA Responders

Responder definition	PREVA responder n=	Zolatriptan (doses/14 days)	Summatriptan (doses/14 days)	Oxygen (doses/14 days)	gammaCore plus SoC	SoC	Difference

25%	26	0.8	2.5	3.5	£3,556	£3,899	-£343
40%	20	1.0	3.0	2.8	£3,505	£3,899	-£394
50% using means	32	1.6	2.8	6.5	£3,795	£3,899	-£104
50%	17	0.6	2.5	2.2	£3,448	£3,899	-£450
65%	10	0.0	2.0	0.7	£3,387	£3,899	-£512

The scenario with the lowest cost saving is where the resource use is based on the mean resource use across the whole of the gammaCore arm, as was presented in Morris et al. (2016). In this scenario the first three months are cost saving, as gammaCore is provided free of charge, however the cost-savings are lower than other scenarios since the gammaCore non-responders have SoC resource use. In all of the subsequent months gammaCore is slightly cost incurring, due to increases across all medication types from the base case. Over a year the model still finds gammaCore as cost saving.

The second group of scenarios modelled are using different rates of reduction in gammaCore use, so that its use gradually approaches zero at the end of 1 year. This is reproduced for all the variations in responder definition, and reduces the cost saving slightly in each case.

The third group of scenarios modelled uses the PREVA gammaCore baseline medication use for the gammaCore non-responders rather than reverting to standard care values. This is reproduced for all the variations in responder definition and increases the cost saving in each case.

4.7 Interpretation of economic evidence

The company's interpretation of economic evidence included a description of the differences between Morris et al (2016) and submission.

The key differences are that the submitted model provides a free 3 month trial, and the change from using the mean value of medication use for the whole gammaCore arm, rather than just for the responder group.

If gammaCore were not provided free of cost for the initial 3 months, the model would not be cost saving.

The company state that Morris et al. (2016) modelled costs that were less generalisable to clinical practice and abortive medication use conditional on responder status was less robust.
It is hard to comment on the robustness of the data as we do not have sufficient information; this analysis is not included in the published papers. It should be noted that both Morris et al. (2016) and Jenks et al (2016) found gammaCore to be cost incurring in the UK although using different modelling approaches (and for Jenks et al, 2016) a slightly different population. Morris et al (2016) did not include a free trial period, although there was a cost-free period included by Jenks et al (2016).

4.8 Results of EAC analysis

The EAC have not made any changes to the base case submission, but have added some extra fields into the sensitivity analysis and scenarios.

Although there are some uncertainties about the data used and the appropriateness of the patient population, the EAC have not identified an alternative, more robust data source that could be used in this patient population, in this setting.

Base-case analysis results

The EAC did not alter the base case results

Sensitivity analysis results

Additional scenarios were run where the model was changed to remove the cost free 3 month trial. This was applied to all the company scenarios. The only scenarios that remained cost saving were those where gammaCore non-responders baseline medication use was used for the gammaCore non-responder group, rather than values from the standard care arm. The EAC believe that the use of the standard care medication use (as is calculated in the submitted base case) for gammaCore non-responders is the more realistic option. Thus, without the free trial, gammaCore would not be cost-saving.

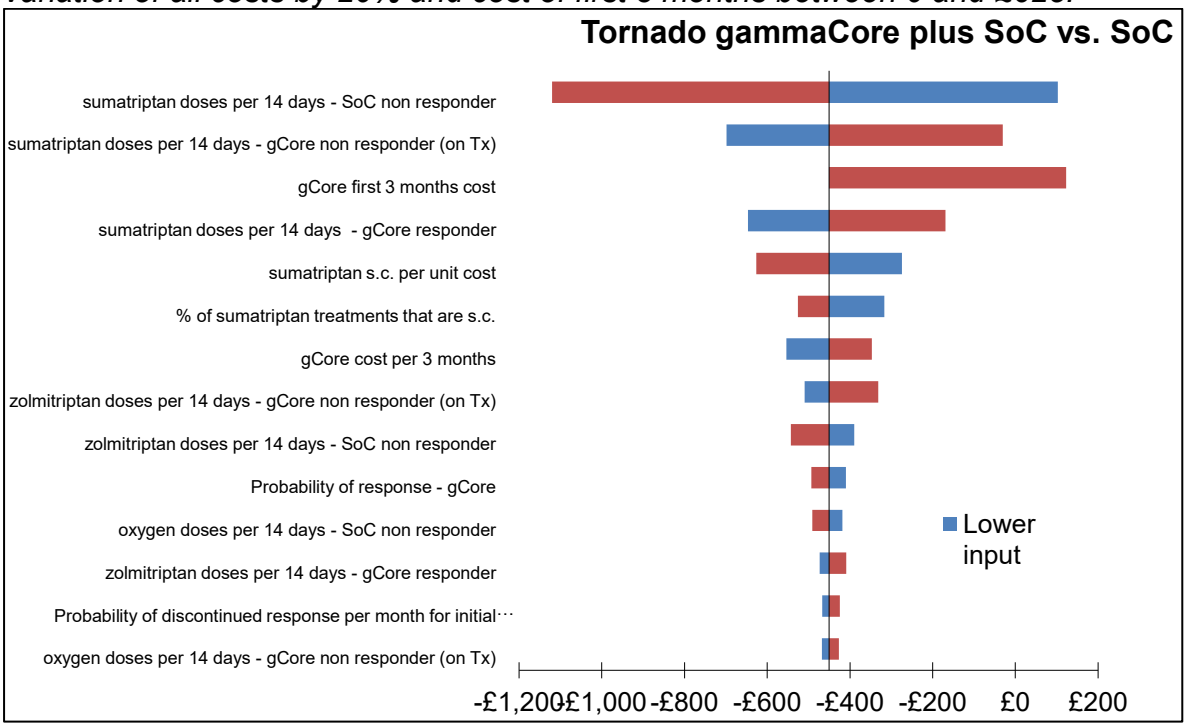
In all scenarios, the bulk of the cost saving occurs in the first 3 trial months. Following this the model is slightly cost-saving in the base case, in some other scenarios it is slightly cost-incurring each month (after the free trial), however these costs do not increase sufficiently in one year to make the overall model cost incurring.

The previous model by Morris et al (2016) did not have a free 3 month trial, and this is likely to be one of the major causes of the cost incurring result.

Where the one-way sensitivity analysis is re-run with the free trial maintained, but gammaCore costs varying by 20% in either direction (low £500, high £750) the gammaCore cost comes into the tornado diagram as the 5th largest change. It still remains cost saving at both of these values.

If we include 20% variation on all costs, and allow gammaCore 1st 3 months to vary between 0 and £625 the following results are seen:

Figure 2 EAC tornado diagram using the submitted base case and including variation of all costs by 20% and cost of first 3 months between 0 and £625.



This confirms the idea that the gammaCore costs and sumatriptan use/costs are the key drivers of the model, and that the cost saving depends on a reduced use of Sumatriptan and the free trial at the start of gammaCore use.

Subgroup analysis

The EAC did not complete any sub-group analysis.

Model validation

There is no detail provided of the validation by clinical experts. The model is based on the previously published model resulting from the PREVA study. This has been published in a peer reviewed journal (Morris et al. 2016), and reported costs from a German perspective. This model found gammaCore to be cost saving, however the scenario from a UK perspective found gammaCore to be cost incurring (although cost effective). The publication gave no details of the adaptation, however in correspondence with the EAC the authors stated that the only changes were to use UK prices and utilities.. The authors of Morris et al. 2016 include representatives from the company and the group who developed the submitted model, and therefore is not an independent validation of the submission results. All identified economic models and clinical inputs to the model are co-authored by the company. and in most cases have received funding from the company.

4.9 EAC Interpretation of economic evidence

The EAC have not made changes to the structure or assumptions in the model. Although there are uncertainties in the data and inputs, we do not have additional data available that would give a more robust base case.

The EAC have considered the model structure and inputs, together with input from expert advisors, previous models and other clinical papers. As a result the EAC have investigated possible changes or scenarios to understand how much emphasis and certainty to place on the modelled results. The scenarios are not presented in full, as none of them had sufficient justification to change the base case, given the information available. Additional scenarios were modeled during quality assurance of the model, including scenarios that are

not clinically realistic. Again, these assist in understanding the model, and are presented in Appendix G.

Changes considered by the EAC, the rationale for them and the possible impact are in table 12

Table 12: Changes considered by the EAC

Potential change	Rationale	Potential Impact
Use the 50% with means as base case	This is the only publically available clinical data from PREVA for this population. This data reduces the possibility of bias due to selecting sub-groups for post-hoc analysis.	Modelled as a scenario in the submission, decreases cost saving
Gammacore non-responder costs for first 3 months – is it reasonable to still reduce medication use for this group?	Non-responders will include anyone with a response rate of less than 50%, and it is therefore reasonable to include a reduction in medication for attacks.	Removing this would reduce the gammaCore cost saving, but only slightly
Initial set up costs of gammaCore and the cost of review appointments.	This has been considered but most expert views to date point to reviews being included in routine appointments Jenks et al (2016) included the cost of a nurse appointment to discuss gammaCore with potential patients, with 1.9 appointments per patient who took up gammaCore use	Modelling to include a review appointment and initial nurse discussion was included in the QA scenarios. The model remained cost saving, but at a reduced amount.
Introduce a third state of partial responders	This could be used to understand the impact of patients with only a small effect from gammaCore still wishing to continue using it.	

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC did not make any changes, however the table 12 illustrates changes that were considered and the potential impact they could have.

5 Conclusions

5.1 Conclusions on the clinical evidence

The evidence is comprised of a small number of studies including randomised trials and observational studies with UK specific evidence limited to observational data. All but one of the published studies (Trimboli et al, 2018) have company involvement in terms of data collection, analysis and authorship however the EAC acknowledge that the prevalence of cluster headaches is very low therefore it is unlikely that large randomised trials would be possible.

Overall the published evidence suggests that patients with cluster headache may benefit from using GammaCore however the degree of benefit is not clear and as none of the studies follow-up for more than a few weeks, there is no evidence of whether any benefit is sustainable long term.

There is some evidence from two randomised trials (ACT 1 and ACT 2) that patients with episodic cluster headache achieve a better response compared with patients with chronic cluster headache however the trials were not powered for this subgroup analysis so these results should be considered with caution, particularly as when considering the whole cohort (episodic and chronic) the benefit of gammaCore was not significant. In addition, the PREVA trial included chronic cluster headache patients only and reported a significant benefit of gammaCore.

Pooled analysis of the data from the ACT1 (Silberstein et al, 2016) and the ACT2 (Goadsby et al, 2018) trials suggest that episodic cluster headaches achieve a significantly better response with nVNS compared with Sham treatment but this did not extend to patients with chronic cluster headaches.

It is important to consider that in all three trials, gammaCore was used in addition to standard care and not in treatment refractory patients. The ACT 1 and ACT 2 trials used gammaCore as an acute treatment in addition to standard care and the PREVA trial used gammaCore prophylactically as an adjunct to standard care. It is therefore possible that the benefit to patients lies in the addition of gammaCore to their current treatment.

5.2 Conclusions on the economic evidence

The key premise of the submitted model is that

- The only additional costs incurred when a patient commences using gammaCore are 3 monthly prescriptions after a free 3 month trial.
- Patients who respond to gammaCore will have a reduced level of medication use for acute attacks, particularly for Sumatriptan.
- Patients who do not have the defined response rate will stop using gammaCore and revert to standard care.

With the current structure even if no patients meet the threshold to be defined as responders, the model would show a very small cost saving. This is because there is no cost to gammaCore modelled during the 3 month trial, and there is a small reduction in medication use for non-responders who are using gammaCore. After 3 months the ongoing costs would be the same in each arm, as no patients would be using gammaCore

The model relies on the free trial and the reduction in sumatriptan to give a cost-saving result at one year. Were the price structure to change and the free trial be withdrawn, or, if the reduction in sumatriptan were not realized, then the model would no longer be cost saving.

The model is very robust to the submitted sensitivity analysis and alternative scenarios, but relies totally on part of a single small data set, only partially based in the UK, with extensive unpublished post-hoc analysis.

6 Summary of the combined clinical and economic sections

The EAC concludes that there may be some patients who benefit from using gammaCore as a prophylactic and/or acute treatment for cluster headaches although the extent of the benefit is less clear at this time both in terms of the degree of response and duration of response.

GammaCore may lead to cost savings however this is highly dependent on the availability of the free three month trial provided the company and reductions in use of other medications use, primarily sumatriptan

7 Key Considerations

The EAC have identified some key areas for discussion and consideration which are outlined in table 13.

Table 13: Key Considerations

Key Point for Consideration	Consider
All but one of the studies in the clinical submission have company involvement and the one independent study is the only study which reported negative results.	Randomised trials may not happen without support from the company, however the degree of involvement from the company should be considered and any role in research clearly defined.
Current published evidence comprises only 3 randomised trials and 4 cohort studies all with a number of methodological concerns which potentially limit their usefulness	Prevalence of cluster headache in the UK is very low. A large, UK based, blinded randomised trial is unlikely to be possible
Only two of the published studies are in a population restricted to treatment refractory patients and only one of those provides a definition of treatment refractory	Is it possible that the clinical pathway and the place for GammaCore needs more discussion however careful consideration to ensure the pathway is being defined according to clinical need rather than evidence availability.
All results are based on patient reported outcomes which, while appropriate, may be subject to bias	Patients are the best judge of whether their condition is improving or not so patient reported outcomes are the most appropriate however consider the possibility of placebo effects, possible bias (recall etc).

Subgroup analyses were conducted in two randomised trials, looking at results in episodic cluster headache and chronic cluster headache separately	Results should be interpreted with caution as the studies were not powered for subgroup analysis. Consider how the results from ACT 1 and ACT 2 compare with results from other studies however it is important to note that although other studies found clinical benefit in chronic cluster headaches, there are differences in methodology and use of gammaCore.
Extensive post-hoc analysis of patients into responder / non-responder groups was used to calculate resource use in the model.	There is a possibility of introducing bias by additional post-hoc analysis of data. Not all patients are included (as not all had resource data), and the number of included patients in the post-hoc analysis and Gaul at al.(2016) differ.
The cost-saving depends on the availability of a free trial period	This should be clearly understood by future users.

8 Implications for research

The EAC considers the possibility of a large, blinded randomised trial would be difficult to achieve in the UK given the low prevalence of the condition. For this reason the EAC considers that a clinical audit would be the most appropriate way to generate evidence.

Key information should include

- A clear definition of the clinical pathway and where gammaCore is intended to fit based on most likely benefit.
- Consideration should be given to potential subgroups that might benefit differently, for example treatment refractory patients, patients with chronic cluster headache, patients with episodic cluster headache

- Long term follow up data should be collected and reported to investigate whether any benefit from gammaCore is sustained over time

- Outcome data should be clearly defined not just in terms of the outcome itself but also in terms of the unit of measurement so that data from different centres can be collated and analysed effectively.

- A standardised method through which to measure patient response and compliance with treatment protocols should be defined.

- Potential confounding factors, such as co-morbidities and other medications, and their effect should be considered.

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9 Appendices

Appendix A - Company and EAC literature search strategies and PRISMA diagrams

Company search strategy for clinical evidence and adverse events

The Medline and Medline In-Process databases were searched through PubMed.gov using the Entrez service provider. The Embase and Cochrane Library databases were searched using the OVID and Wiley service providers, respectively. Searches were limited to articles published between 1 January 2005 and 21 February 2019 for clinical evidence and 6 March 2019 for adverse events.

Search terms for clinical evidence were (“headache” OR “migraine” OR “cardiovascular”) AND (“non-invasive vagus nerve stimulation” OR “noninvasive vagus nerve stimulation” OR “gammaCore” OR “transcutaneous vagus nerve stimulation”) AND ("safety" OR "safe" OR "tolerability" OR "side effect" OR "adverse event"). In the PubMed search, “humans” was used as a MeSH term, language was specified as English, and no search limits on article type were defined to ensure the identification of all relevant studies, including clinical trials and real-world and observational studies. In Embase, the Title or Abstract field was used to search for the terms, and results filters were applied for diseases (migraine, headache, chronic cluster headache, episodic migraine, cluster headache, transformed migraine, migraine without aura, primary headache, episodic cluster headache, menstrual migraine, migraine with aura, and drug induced headache), study types (humans), and publication types (article). In the Cochrane Library, the All Text field was used to search for the terms, and a search limit was defined to identify trials only.

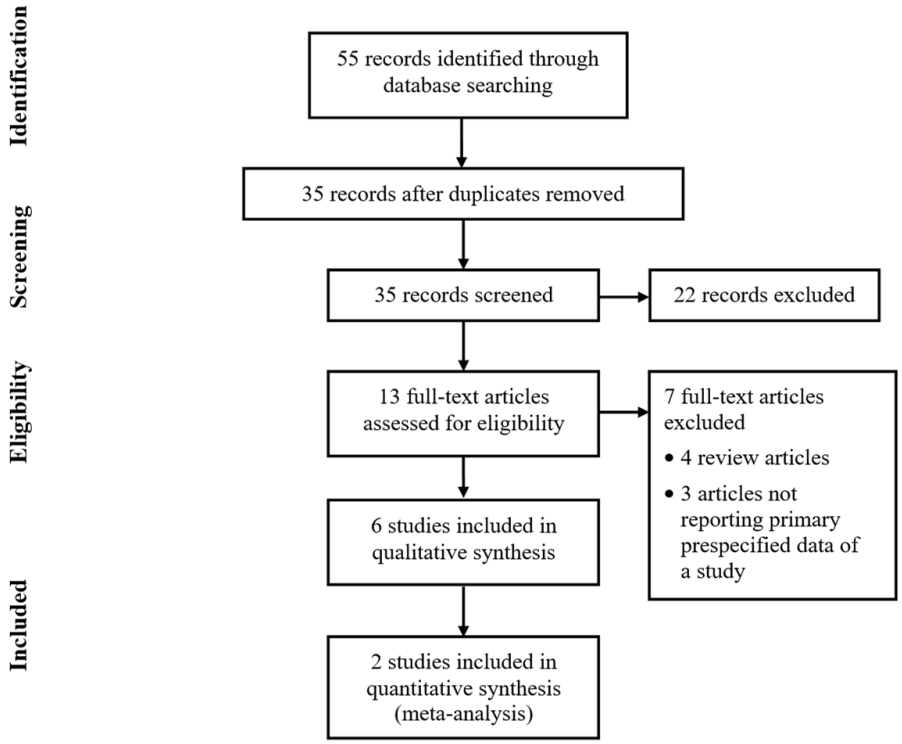
Search terms for adverse events were (“headache” OR “migraine” OR “cardiovascular”) AND (“non-invasive vagus nerve stimulation” OR “noninvasive vagus nerve stimulation” OR “gammaCore” OR “transcutaneous vagus nerve stimulation”) AND ("safety" OR "safe" OR "tolerability" OR "side effect" OR "adverse event"). In the PubMed search, “humans” was used as a MeSH term, language was specified as English, and no search limits on article type were defined to ensure the identification of all relevant studies,

including clinical trials and real-world and observational studies. In Embase, the Title or Abstract field was used to search for the terms, and results filters were applied for diseases (migraine, headache, chronic cluster headache, episodic migraine, cluster headache, transformed migraine, migraine without aura, primary headache, episodic cluster headache, menstrual migraine, migraine with aura, and drug induced headache), study types (humans), and publication types (article). In the Cochrane Library, the All Text field was used to search for the terms, and a search limit was defined to identify trials only.

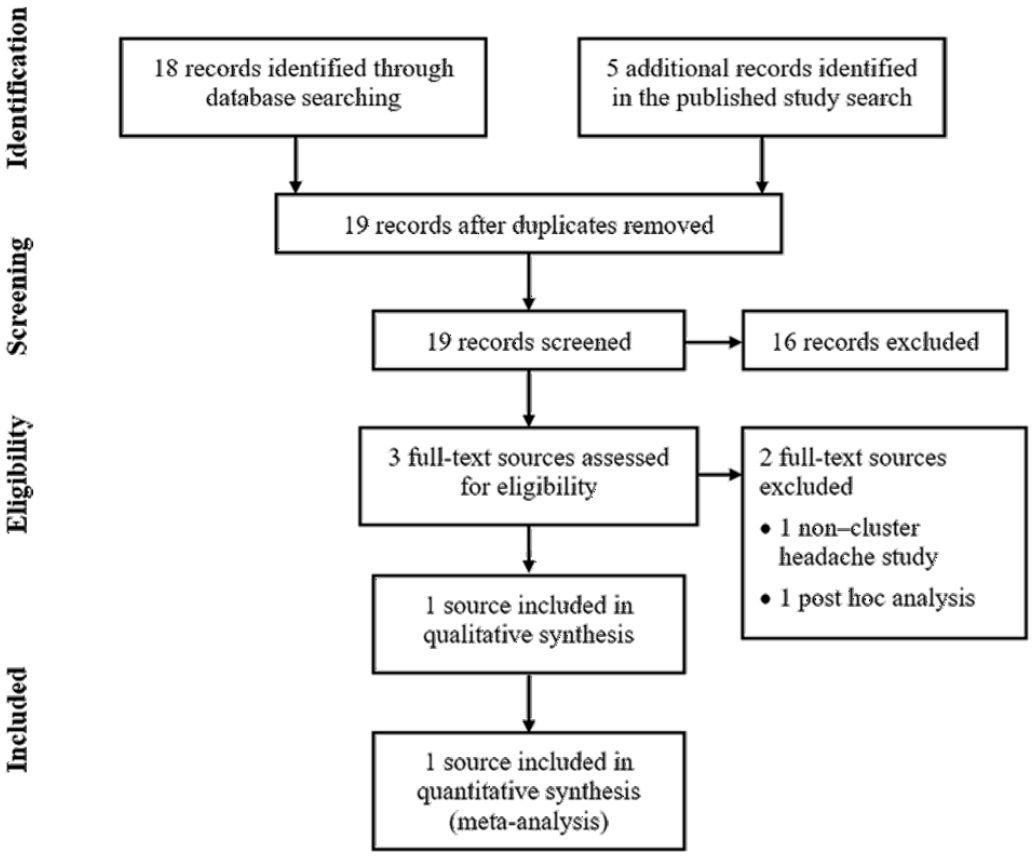
To identify unpublished studies the company searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) databases.

The company also searched their own publically available repository of conference abstracts.

Company's PRISMA diagram for published studies of nVNS for cluster headache



Company's PRISMA diagram for unpublished studies of nVNS for cluster headache



EAC search strategy for clinical evidence and adverse events

The EAC designed a search strategy in Medline (Ovid) incorporating the main elements of the scope, presented below, and translated it to the databases listed in the table below. One strategy was designed to identify published clinical evidence, evidence reporting adverse events and economic evidence. Citation tracking of the EAC's included clinical papers (Gaul et al. 2016, Gaul et al. 2017, Goadsby et al. 2018, Marin et al. 2018, Nesbitt et al. 2015, Silberstein et al. 2016, Trimboli et al. 2018) was conducted in Google Scholar.

Date	Database Name or Resource	Total Number of records retrieved	Total number of records loaded into Endnote (Duplicates not imported)	Total number of records from databases after de-duplication
20/03/19	Medline All (Ovid)	34	34	
28/03/19	Embase (Ovid)	76	59	
28/03/19	The Cochrane Library (Wiley) CDSR CENTRAL	 0 27	10	
28/03/19	CRD databases: DARE HTA NHS EED	0	0	
28/03/19	Scopus (Elsevier)	36	15	
28/03/19	Web of Science (SCI-EXPANDEDCPCI-S, ESCI)(Clarivate Analytics)	49	16	
28/03/19	Pubmed	27	20	
				124
28/03/19	MHRA	0	0	
28/03/19	MAUDE	1 (same as company submission)	0	
28/03/19	Clinical Trials.gov	3 (all completed, no ongoing studies)	0	
28/03/19	ICTRP	0	0	
28/03/19	Citation Tracking of: Gaul 2015, Gaul 2017, Goadsby 2018, Marin 2018, Nesbitt 2015, Silberstein 2016, Trimboli 2018, Jenks et al. 2016, Morris et al. 2017, Mwamburi et al. 2017a in Google Scholar Limited to >/=2018	0 additional relevant records	0	
24/04/19	Mwamburi et al. 2017b – included studies checked for relevance	1	1	125

Ovid MEDLINE(R) ALL <1946 to March 19, 2019> Search Strategy:

1 "cluster headache*".tw. (2903)

2 trigeminal autonomic cephalalgias/ or cluster headache/ (2645)

3 1 or 2 (3568)

4 gammacore.tw. (18)

5 "non-invasive vagus nerve stimulation".tw. (43)

6 nVNS.tw. (55)

7 Transcutaneous Electric Nerve Stimulation/ (4366)

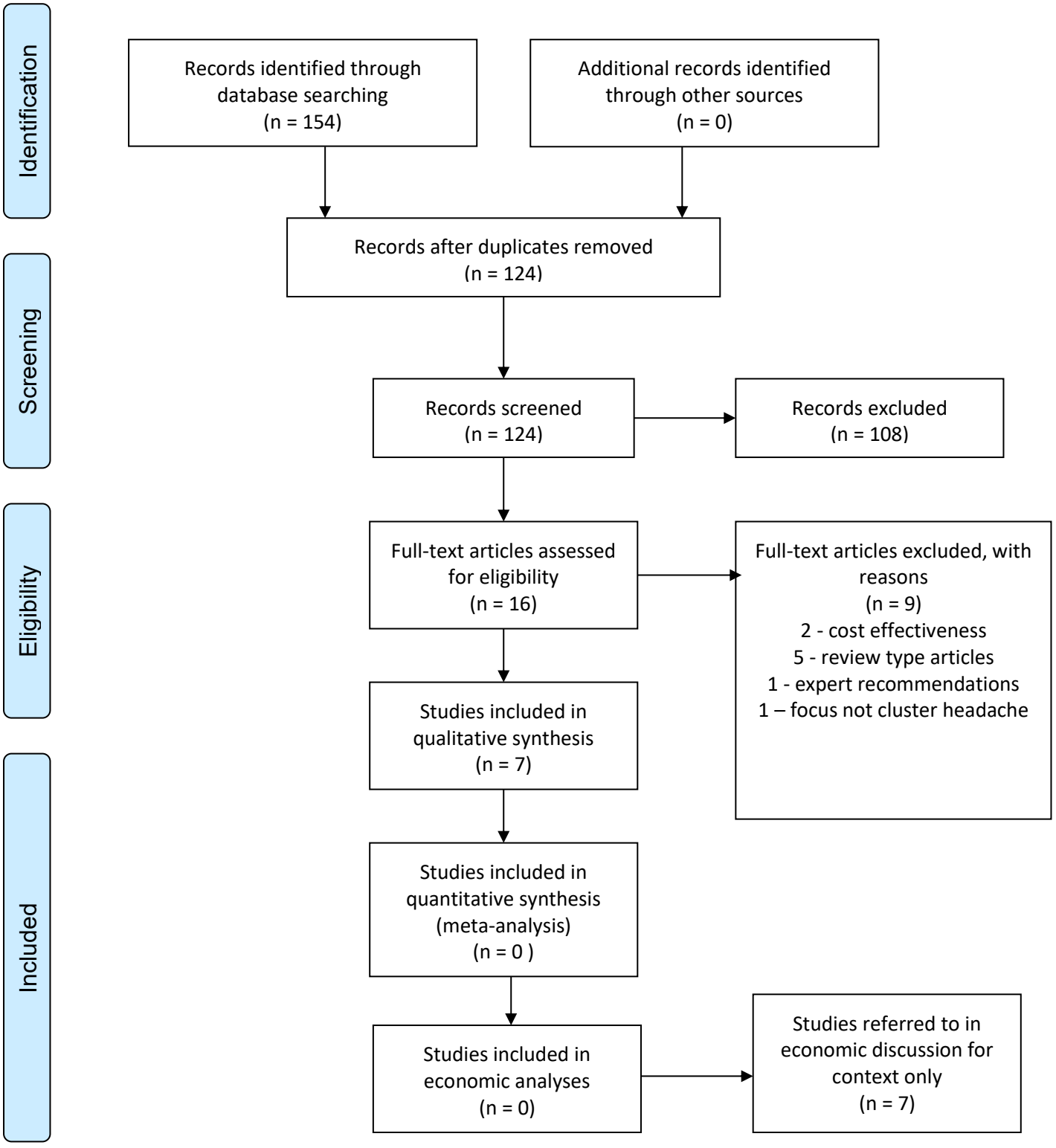
8 "transcutaneous vagus nerve stimulation".tw. (85)

9 "noninvasive vagus nerve stimulation".tw. (19)

10 or/4-9 (4485)

11 3 and 10 (34)

EAC's PRISMA diagram for clinical and economic published studies of nVNS for cluster headache



Appendix B: Data Extraction Tables for Included Studies

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
Objective	To evaluate non-invasive vagus nerve stimulation (nVNS) as an acute CH treatment	To confirm and extend the results from ACT 1 by examining additional outcomes	To examine non-invasive VNS (nVNS) as adjunctive prophylactic therapy for CH attacks in patients with chronic cluster headache.	To investigate the time to therapeutic benefit onset and the response rate levels associated with adjunctive nVNS used in cCH prophylaxis	To audit the usefulness of a non-invasive nVNS device in patients with cluster headache	To audit real-world data from patients with CH, the majority being treatment refractory, to explore early clinical experience with nVNS used acutely, preventatively or both.	To assess whether non-invasive neurostimulation approaches such as nVNS, have a role in the CH treatment pathway before considering invasive neurostimulation procedures
Location	USA (20 centres)	Four European Countries including the UK (9 tertiary care centres)	10 European sites including 3 in the UK	10 European sites including 3 in the UK	Tertiary headache centre in the UK	10 clinical centres in the UK	Headache Centre at a UK hospital
Design	Randomised double-blind, sham controlled prospective study	Randomised, double blind, Sham Controlled Trial	Randomised, multi-centre, open label, parallel group study. NCT: 01701245	***Post-hoc analysis of data from a*** randomised, multi-centre, open label, parallel group study	Clinical audit of patients treated with non-invasive nVNS device (gammaCore). Non-comparative study	Retrospective data analysis (non-comparative)	Prospective cohort study
Duration of study	February 2013 to October 2014 Double blind phase (1 month)	September 2013 to October 2014 1 week run in period 2 week double blind period	October 2012 to March 2014 2 week run in period 4 week open label randomisation period	October 2012 to March 2014 2 week run in period 4 week open label randomisation period	January to December 2012	May 2012-March 2016	January 2014-August 2016

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	Open label phase (3 months)	Open label period	Optional 4 week period where all participants could have nVNS plus standard care	Optional 4 week period where all participants could have nVNS plus standard care			
Patient population	N=150 Randomisation: 1:1 using variable block design (stratified by site). Trained study site personnel allocated the devices Investigators, participants and study co-ordinators were blinded	N=102 Randomisation: 1:1 using a standard design with a block size of 4 using sealed envelopes. Unblinded trainers provided the appropriate device to patients	N=114 Randomisation: 1:1 by standard block design to receive either standard care (SoC) plus nVNS or standard care alone.	N=97 patients who were randomised as part of the PREVA study.	N=25 patients with cluster headache	N=30 patients with cluster headache (29 with cCH)	N=42 consecutive medically refractory patients meeting the ICHD criteria for CM and TACs N=12 with cCH
Sample size	A sample size of 120 participants was determined to provide 82% power ($p \leq 0.05$ for a two sided test). A planned enrolment of 150 participants would allow for a 20% attrition rate.	A sample size of 54 participants per group was calculated to provide 80% power (primary outcome) based on 10% dropout rate and assuming a response probability of 0.3 for the Sham group and 0.6 for the gammaCore group	A sample size of 40 participants per arm was calculated to provide 80% power to detect a difference between the outcomes for the primary outcome using a two sided test with $\alpha \leq 0.05$.	No sample size calculation for these outcomes as it is a post-hoc analysis. A sample size calculation was done for the primary outcome in the original trial but is not appropriate to this analysis.	No sample size calculation reported	No sample size calculation reported	No sample size calculation reported

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
			Enrolment of 90 with a 10% dropout was planned Mean frequency of CH attacks was estimated at baseline to be 4.0 per week Predicted reductions in number of CH attacks were 50% for SoC+nVNS and 10% for SoC alone.				
Inclusion criteria	Aged 18-75 years diagnosed with eCH or cCH according to ICHD 2nd edition	Aged ≥18 years with a diagnosis of episodic or chronic cluster headache as defined by ICHD criteria	Aged 18-70 years with a diagnosis of chronic cluster headache ≥1 year prior to enrolment according to ICHD	Aged 18-70 years with a diagnosis of chronic cluster headache ≥1 year prior to enrolment according to ICHD	No details Appears to use ICHD definition of CH Appears to have no age limit on participation (one participant was aged 13 years)	Previous inadequate response and/or intolerable side effects with ≥3 current or previous CH treatments Appears to use ICHD definition of CH Appears to have no age limit on participation (age range is 16-72 years)	Patients with refractory CM of cCH based on EHF recommendations

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
Exclusion criteria	• History of aneurism, intracranial haemorrhage, brain tumours, significant head trauma, prolonged QT interval, arrhythmia, ventricular tachycardia/fibrillation, syncope or seizure; structural intracranial/cervical vascular lesions; another significant pain disorder, • cardiovascular disease, uncontrolled hypertension, abnormal baseline echocardiogram, • botulinum toxin injections in the past 3 months,	• Individuals with eCH who were not in a bout at the time of screening • Pregnant, nursing or planning pregnancy • Abnormal baseline electrocardiogram	• Change in prophylactic medication type or dosage <1 month before enrolment • History of intracranial/carotid aneurysm or haemorrhage • Brian tumours or lesions • Significant head trauma • Previous surgery or abnormal anatomy at the nVNS treatment site • Known or suspected cardiac/cardiovascular disease • Implantation with electrical or neurostimulation devices • History of carotid endarterectomy or vascular neck surgery	• Change in prophylactic medication type or dosage <1 month before enrolment • History of intracranial/carotid aneurysm or haemorrhage • Brian tumours or lesions • Significant head trauma • Previous surgery or abnormal anatomy at the nVNS treatment site • Known or suspected cardiac/cardiovascular disease • Implantation with electrical or neurostimulation devices • History of carotid endarterectomy or vascular neck surgery	• Active neurostimulation devices • Cardic pacemakers • Significant history of autonomic disorders or cardiac arrythmia	• Patients who were no longer experiencing attacks at the time of analysis were excluded from analysis of attack duration and severity • Data from patients who lacked quantitative information regarding attack duration and severity were included only in qualitative analysis of these variables	• Active neurostimulation devices • Cardiac pacemakers • Significant history of cardiac arrythmia

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	• nerve blocks in the past 1 month, • previous CH surgery, bilateral/right cervical vagotomy, carotid end arterectomy or right vascular neck surgery, electrical device implantation • Current use of prophylactic medications for indications other than CH		• Implantation with metallic hardware • Recent history of syncope or seizures	• Implantation with metallic hardware Recent history of syncope or seizures			
Intervention(s) (n =) and comparator(s) (n =)	*Intervention: N=73* nVNS device (gammaCore) which produces a proprietary low voltage electrical signal comprising a 5-kHz sine wave burst lasting 1 millisecond (5 sine waves, each lasting 200 microseconds),	Run In Period – 1 week n=102: all participants maintained their established standard of care Double Blind Period: 2 weeks	Run in period – 2 weeks N=114: all participants continued with their standard of care 17 exclusions/discontinuations	nVNS+SoC = 48 SoC = 49 Three 2minute stimulations (i.e. three doses) five minutes apart administered twice daily (i.e. six doses per day) to the right	N=19 nVNS in addition to their current treatment plan.	N=30 patients who were treatment refractory given nVNS Initial nVNS dosing was based on established paradigms and titrated as	N=12 patients using nVNS as preventative and abortive treatment 2 consecutive nVNS doses (90 seconds each) on one side of the neck or alternating right

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	repeated every 40 milliseconds (25Hz) 3 consecutive 2 minute stimulations to the right side of the neck at onset of symptoms or pain Only one attack in a 12 hour period could be treated during the double blind phase (no limits during open label phase) Abortive or pain-relieving medication was permitted at least 15 minutes after initiation of nVNS treatment *Comparator: N=77* Sham device which looks/feels identical to intervention but produces a low frequency, biphasic signal and does not	GammaCore + SOC: n=50 Standard of Care: n=52 Open Label Period: 2 weeks GammaCore + SOC: n=45 Standard of Care: n=38 3 consecutive 120 second stimulations ipsilateral to their CH attack at the time of attack onset with 3 addition stimulations permitted if attack was not aborted within 9 minutes of treatment initiation. A minimum of 6 hours between nVNS treatments was required. Abortive or pain-relieving medication was permitted at least 15 minutes	Open Label Randomisation period – 4 weeks nVNS + SoC=48 (ITT=45) SoC=49 (ITT=48) Extension Phase – 4 weeks nVNS+SoC=44 SoC=48 End of Study nVNS+SoC=33 SoC=37 Three 2minute stimulations (i.e. three doses) five minutes apart administered twice daily (i.e. six doses per day) to the right	side of the neck (right vagal nerve). Participants also had the option of acutely treating CH attacks with three additional nVNS doses at pain onset but were advised to not administer prophylactic therapy within a two-hour period after acute treatment Abortive or pain-relieving medication was permitted at least 15 minutes after initiation of nVNS treatment	Up to 3 consecutive doses to treat an attack acutely. 2 (and in some cases 3) consecutive doses in the morning and late afternoon (approximately 8 hours apart) daily for preventative treatment	necessary to achieve maximum benefit.	and left sides, three times a day, as a preventive stimulation paradigm. Up to 3 additional consecutive doses before resorting to their usual abortive treatment for acute treatment.

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	stimulate the vagus nerve.	after initiation of nVNS treatment	side of the neck (right vagal nerve). Participants also had the option of acutely treating CH attacks with three additional nVNS doses at pain onset but were advised to not administer prophylactic therapy within a two-hour period after acute treatment Abortive or pain-relieving medication was permitted at least 15 minutes after initiation of nVNS treatment				
Baseline differences **Cohort Demographics**	Baseline characteristics were similar between the groups and were, according to the authors,	Generally similar between groups *Study cohort* • 75% male • 99% White	Demographics and baseline characteristics were similar between the two groups and were considered by the authors to be	Demographics and baseline characteristics were similar between the two groups and were considered by the authors to be	No comparator at baseline N=11 male, median age 49 years	No comparator at baseline N=19 (63%) female N=29 (97%) cCH	No comparator at baseline N=7 female, median age 49.5 years

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	representative of a CH population. *Study Cohort* • 84% male • 87% White • 67% eCH and 33% cCH • 64% used triptans and 14% used oxygen to manage CH • Other medications included mild analgesics, narcotics, verapamil, lithium, topiramate, and corticosteroids	• 30% eCH and 70% cCH • 69.4% used triptans and 56.8% used oxygen to manage CH • Other medications included mild analgesics, narcotics, verapamil, lithium, propranolol, tricyclic antidepressants, serotonin receptor antagonists, anti-epileptics and corticosteroids	representative of the CH population. *Study Cohort* • 69% male • 52.5% used verapamil/verapamil chloride, 89.6% used pharmacological medications and 68% used oxygen to manage cCH • Other medications included lithium/lithium carbonate, topiramate and corticosteroids	representative of the CH population. *Study Cohort* • 69% male • 52.5% used verapamil/verapamil chloride, 89.6% used pharmacological medications and 68% used oxygen to manage cCH Other medications included lithium/lithium carbonate, topiramate and corticosteroids	N=11 cCH (7 male; median age 52 years) N=8 eCH (4 male; median age 46 years)	Mean failed preventative treatments=8.9 Mean failed acute treatments=1.3	
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of	Not clear Baseline screening but not clear if this was a visit/phone call etc.	Patient visits Visit 1: Baseline visit for screening Visit 2: End of run in period Visit 3: End of double blind period	Not Clear Appears to be scheduled clinic visits with patients keeping self-recorded diaries however no details of	Not Clear Appears to be scheduled clinic visits with patients keeping self-recorded diaries however no details	No details Diaries were kept by patients but authors state: "Given the incomplete nature of diaries over a 1 year	Not clear Patient diaries Medical records Patient interviews Treatment diaries	Outpatient visits at baseline and 3 months

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
follow-up, participants lost to follow-up	Participants used diaries to record • pain intensity (rated at 15 mins, 30 mins, 1 hour and 2 hours after treatment) • attack duration • rescue medication use • AEs • Device perceptions • Blinding questionnaire responses for each attack	Participants also self-recorded using paper diaries.	any visits are given apart from a mention of scheduled clinic visits when discussing AEs.	of any visits are given apart from a mention of scheduled clinic visits when discussing AEs.	period of observation, we preferred a patients broad estimate of the benefit"	Physician notes documented during the nVNS evaluation period	
Statistical tests	Analysis was on Intent to Treat basis • Attack duration and device perception	Demographic and baseline data: quantitative variables summarised using descriptive statistics, qualitative variables	Safety and tolerability were assessed in the safety population (all participants assigned to treatment)	All analyses used the modified intent to treat population (mITT) defined as subjects with data available for each study week.	Summary data presented as mean ± standard error (SE)	Descriptive Statistics Paired t-test to assess within	No details reported but results presented using descriptive methods

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	analyses were conducted on observed cases with attacks lasting >180 minutes excluded. • Descriptive statistics used for continuous variables • Frequency distributions and proportions used for categorical variables • Clopper-Pearson 95% CI calculated for response rates. • Fishers exact or Chi square test to test for differences between groups. • Linear mixed effects regression models were	by counts and percentages. Double blind period Primary end point was evaluated using generalised estimating equations (treatment group (cCH & eCH) and study site (cCH) were independent factors), a type 3 fixed effects evaluated the interaction between treatment type and CH subgroup. Wilcoxon rank test (stratification by study site) to compare mean proportion of treated attacks 2 sided t-tests to test for changes in mean pain intensity	Intent to Treat (ITT) Population: participants with ≥1 efficacy recording in the headache diary after randomisation. Modified ITT population: participants who had measurable observations across respective study phases being compared (i.e. baseline vs. randomised; baseline vs. extension or randomised vs. extension). Analysis of variance and analysis of covariance were used to address differences between treatment groups for the primary end-point and the change in duration and intensity of CH attacks	t-test for mean weekly attack frequency and global percentage change in weekly attack frequency Fisher exact and chi square test for response rates.	Midpoint of ranges reported Frequency data compared using a general linear model	patient changes from baseline	

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	used to compare mean treatment group intensities • t-test for attack duration comparisons • NcNemar test for paired proportions to compare within-subject response rates between the double blind and open label phases • Missing data were imputed as failures for response variables and using the last observation carried forward for attack intensity.	Fisher exact test to compare patients achieving pain free status	Wilcoxon rank sum test to assess within participant differences in number of CH attacks and pain intensity Chi square test to evaluate difference in response rates between treatment groups Two sided p values were calculated P<0.05 was considered statistically significant				
Primary outcomes (including scoring	Response rate assessed in the double blind phase (proportion of	Proportion of all treated attacks achieving pain free	Reduction in the mean number of CH attacks per week, defined as the	Mean weekly attack frequency over time Global percentage change from	• Perceived overall change in condition from baseline	• nVNS use • Attack frequency,	• Response Rates (defined as ≥30%

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
methods and timings of assessments)	participants achieving a pain intensity score of 0 or 1 on a 5 point scale at 15 minutes after treatment initiation for first CH attack) Rescue medication within 60 minutes was considered treatment failure.	status within 15 minutes	number of attacks during the last two weeks of the randomised phase minus the number of attacks during baseline divided by 2. Reductions in mean number of CH attacks per week during the last 2 weeks of the extension phase	baseline in weekly CH attack frequency at the end of the randomised phase Cut-offs of ≥25%, ≥50%, ≥75% and 100% reductions from baseline in attack frequency were used to define response.	• Percentage change in other acute medication use • High flow oxygen and parenteral triptans use while using nVNS device • Proportion of treatments able to terminate within 15 minutes of device use and time to do so	duration and severity • Concomitant treatment use • Safety	reduction in headache days after 3 month treatment) • Change in headache severity including patients subjective impression of change • Treatment compliance • Safety and tolerability
Secondary outcomes (including scoring methods and timings of assessments)	Sustained treatment response (proportion of participants with a pain intensity score of 0 or 1 without rescue medication at 15-60 minutes after treatment initiation for CH attack) Average of all participants mean	Proportion of treated attacks per subject achieving responder status within 30 minutes Proportion of treated attacks per subject achieving pain free status within 30 minutes Mean decreases in pain intensity from	Response Rate: Proportion of patients with ≥50% reduction in mean number of CH attacks per week (assessed during the last 2 weeks of randomisation and last two weeks of extension phases. Abortive medication use		No differentiation between primary/secondary outcomes	No differentiation between primary/secondary outcomes	No differentiation between primary/secondary outcomes

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	pain intensities at 15 minutes after treatment initiation for all attacks (up to 5 attacks per participant). *Safety Endpoints* Serious adverse device effects (SADEs) Adverse Events	attack onset to the 15 and 30 minute timepoints Patients achieving pain free status in ≥50% of treated attacks Adverse events and adverse device effects	Duration and intensity of CH attacks acutely treated with nVNS Number of CH attacks, CH pain intensity (five point scale), CH duration and abortive medication use (assessed through patient completed diaries) Quality of Life (EQ-5D-3L and HIT-6) Adherence to nVNS treatment				
Results	***Results are reported for the double blind phase of the trial only*** N=102 participants were receiving prophylactic treatment at baseline	*Pain free status within 15 minutes* **All CH:** 14% (nVNS) versus 12% (sham), p=0.71 **eCH:** 48% (nVNS) versus 6% (sham), p<0.01	*Effect of nVNS on CH attack frequency* nVNS+SoC showed a greater reduction from baseline compared with SoC alone: -5.9 (SE, 1.2) versus -2.1 (SE, 1.2) giving a mean therapeutic gain of 3.9 fewer CH attacks	*Weekly attack frequency* Mean weekly attack frequency was significantly lower with nVNS+SoC compared with SoC alone (p<0.02) Attack frequencies were significantly	*Treatment Changes during nVNS* N=4 patients had changes made to baseline treatments during nVNS use • 2 had preventative medication withdrawn (1 commenced	*nVNS Use* Mean (range) attack frequency with SoC was 26.6 (3.8-77.0) attacks/week. This decreased to 9.6 (0-38.5) attacks/wk with SoC+VNS (p<0.01)	*Prophylactic Effect* N=1 showed ≥30% reduction in weekly CH frequency at month 3 compared with baseline. This patient also reported a

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	Response Rates **All CH:** 26.7% (nVNS) versus 15.1% (sham), p=0.1 **eCH:** 34.2% (nVNS) versus 10.6% (sham), p=0.008 **cCH:** 13.6% (nVNS) versus 23.1% (sham), p=0.48 *Sustained treatment response rates* **All CH:** 26.7% (nVNS) versus 12.3% (sham), p=0.04 **eCH:** 34.2% (nVNS) versus 10.6% (sham), p=0.08 **cCH:** 13.6% (nVNS) versus 15.4% (sham), p=1.0	**cCH:** 5% (nVNS) versus 13% (sham), p=0.13 *Odds Ratios (95% CI) from the GEE (adjusted for site in the total cohort and in the cCH subgroup)* **All CH:** 1.22 (0.42-3.51), p=0.71 **eCH:** 9.19 (1.77-47.8), p<0.01 **cCH:** 0.41 (0.13-1.30), p=0.13 *Treated Attacks achieving responder status within 30 minutes* **All CH:** 43% (nVNS) versus 28% (sham); p=0.05 **eCH:** 58% (nVNS) versus 28% (sham); p=0.07 **cCH:** 37% (nVNS) versus 29% (sham); p=0.34	per week (95% CI 0.5-7.2; p=0.02) In the mITT, individuals who carried on using nVNS in the extension phase (n=30) reported an additional reduction of two CH attacks per week (9.6 (randomised) versus 7.6 (extension) p<0.001) Addition of nVNS to the control group during the extension phase resulted in a significant reduction in CH attacks (15.7 (randomised) versus 12.4 (extension); p<0.001) *≥50% Response Rates* Response rate was significantly higher in the nVNS+SoC	reduced from baseline beginning at week 1 of the randomised phase and continuing through week 4 of the extension phase (p<0.05) Global mean attack frequency at decreased by 40% from baseline at the end of the randomisation phase in the nVNS+SoC group versus an increase of 1% in the SoC alone group representing a 41% therapeuatic benefit of nVNS (p<0.001). *Response Rates* A significantly higher proportion of patients in the nVNS+SoC group had attack frequency reductions from baseline (≥25% and ≥50% reduction,	methysergide as a substiture and 1 had a pre-existing dose of verapamil increased) • 1 was prescribe high-flow oxygen • 1 discontinued nVNS following a tapering dose of corticosteroids Of this group, 3 had already reported positive but sub-optimal improvements using nVNS and 1 reported no change. *Adverse Events* No SAEs were reported	N=3 patients who had averaged 42-63 attacks/week experienced no attacks during their nVNS evaluation period (1.7 – 13.2 months) Mean duration of attacks decreased from 51.9 (5.0-140.0) minutes with SoC alone to 29.4 (2.5-152.5) minutes with SoC+nVNS; p<0.01 (N=25 patients) Mean attack severity decreased from 7.8 (3.0-10.0) SoC to 6.0 (1.0-10.0) with nVNS+SoC; p<0.01 (n=18 patients)	reduction in oxygen use. N=2 reported a slight improvement from baseline N=3 reported no change N=6 reported a worsening in weekly frequency *Abortive Effect* N=0 reported headache relief using nVNS *Treatment Continuation* N=1 patient continued with nVNS for 10 months but reported a worsening of their condition for 3 consecutive months and discontinued treatment

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	Pain intensity at 15 minutes (double blind phase) **All CH:** nVNS: 2.1 [95% CI 1.9-2.3] versus sham: 2.0 [95% CI 1.8-2.2]; p=0.4 **eCH:** nVNS: 2.0 [95% CI 1.8-2.3] versus sham: 2.0 [95% CI 1.8-2.3], p=1.0 **cCH:** nVNS: 2.3 [95% CI 1.9-2.6] versus sham: 1.9 [95% CI 1.6-2.3], p=0.2. *Responders at 15 mins for ≥50% of treated attacks* **All CH:** 26.7% (nVNS) versus 20.6% (sham); p=0.41 **eCH:** 34.2% (nVNS) versus 14.9% (sham), p=0.04	*Mean decreases in pain intensity from attack onset at 15 and 30 mins (nVNS vs. sham)* **All CH:** 15 mins: -1.3 (0.02) versus -0.9 (0.1); p=0.06 30 mins: -1.6 (0.2) versus -1.2 (0.2); p=0.07 **eCH:** 15 mins: -1.7 (0.4) versus -0.6 (0.2); p=0.01 30 mins: -1.9 (0.4) versus -0.8 (0.4); p=0.03 **cCH:** 15 mins: -1.2 (0.2) versus -1.0 (0.2); p=0.52 30 mins: -1.5 (0.2) versus -1.3 (0.2); p=0.5 *Patients achieving pain free status in*	group compared with SoC alone: 40% (18/45) versus 8.3% (4/48); p<0.001) In the mITT population, response rate was significantly higher in the nVNS+SoC group compared with SoC alone: 48.6% (18/37) versus 8.5% (4/47), p<0.001), suggesting a continued response for participants who remained in the study. During the extension phase, ≥50% response rate was 28.9% for participants continuing with nVNS+SoC and 16.7% for participants continuing with SoC alone.	p<0.001; ≥75% reduction, p<0.009). 3 patients (8%) in the nVNS+SoC group had a 100% attack frequency reduction versus 0% in the SoC group. *Safety and tolerability* No serious device related adverse events Rates of discontinuation were similar between the groups Similar proportions in each group reported ≥1 adverse event.	Two patients reported a side-shifting of attacks One patient reported transient worsening of pain *Prevention* N=15 patients reported overall improvement in their condition from baseline. The remaining 4 reported their condition remained the same. Results suggest a mean improvement of 48%±9% Mean estimated improvement was 62%±8% at 26 weeks and 59%±6% at 52 weeks in 5 patients who had extended follow-up. *Acute treatment: nVNS*	*Concomitant Treatment Use* Patients used a mean (range) of 0.8 (0-2) preventative treatments before initiation of nVNS versus 0.7 (0-2) after nVNS initiation. Mean (range) number of acute treatments used was 1.8 (1-4) before nVNS initiation versus 1.1 (0-2) after. N=22 patients used triptan injection or nasal spray as acute treatment before nVNS initiation; 9 (41%) stopped and 12 (55%) decreased their	*Adverse Events* • No unexpected SAEs • N=5 patients from the whole cohort reported mild to moderate AEs including temporary hoarseness/sore throat, swolled/red skin around the face and neck, nausea, increased frequency of bowel movements/flatus, facial twitching • No patient discontinued treatment due to AEs

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	cCH: 13.6% (nVNS) versus 30.8% (sham), p=0.19 *Pain free at 15 minutes for ≥50% of treated attacks* **All CH:** 11.7% (nVNS) versus 6.9% (sham), p=0.33 **eCH:** 15.8% (nVNS) versus 2.1% (sham), p=0.04 **cCH:** 4.6% (nVNS) versus 15.4% (sham), p=0.36 *Duration of first CH attack (mins)* **All CH:** 50.6±38.3(nVNS) versus 59.9±47.5 (sham), p=0.25 **eCH:** 48.4±35.4 (nVNS) versus 61.2±49.5 (sham), p=0.21	*≥50% of treated attacks after 15 mins* **All CH** 17% (nVNS) versus 7% (sham), p=0.15 **eCH** 36% (nVNS) versus 8% (sham), p=0.16 **cCH** 9% (nVNS) versus 7% (sham); p=1.00 *Patients achieving responder status for ≥50% of treated attacks after 15 mins* **All CH** 40% (nVNS) versus 14% (sham); p<0.01 **eCH** 64% (nVNS) versus 15%; p<0.01) **cCH**	Addition of nVNS to the control group during the extension phase resulted in an increase in response rate from 8.5% (4/47) to 21.6% (8/37). *Abortive Medication Use* A 57% decrease in the frequency of abortive medication use was noted in the nVNS+SoC group (∆= -15 (95% CI: -22.8 to -7.2), p<0.001) compared with (∆= -2 (95% CI: -9.4 to 5.4), p=0.59) in the control arm (% decrease NR). Changes in abortive medication use were driven by reductions in use of SC sumatriptan (p=0.007) and inhaled oxygen (p=0.02). These reductions were		Patients reported that nVNS aborted attacks in an average 11 mins (±1 min) of initial device application This response was stable in 5 patients at 26 and 52 weeks. *Acute Treatment: Changes in previously used approaches* 3 patients stopped using oxygen (n=2) or sumatriptan (n=1) in favour of nVNS. N=10 patients reduced oxygen use by an estimate mean of 55%±8%; 3 continued to use the same amount of oxygen and 1 patient reported an increase by 100% N=3 patients were able to stop using	triptan use during nVNS treatment N=27 (93%) patients reported using high-flow oxygen as acute treatment prior to nVNS initiation; 9 (33%) stopped and 17 (63%) decreased their use Overall, N= 3 patients were able to manage their condition with preventative pharmacological treatment only and N=4 were able to use nVNS as monotherapy *Safety* No SADEs were reported	*Treatment Compliance* Data for 4 CH patients were available and the authors postulate that 1 patient was non-compliant based on when they requested a replacement device.

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	cCH: 54.5±43.8 (nVNS) versus 57.6±44.8, p=0.82 *Change in duration of attacks from baseline to first attack (mins)* **All CH:** -9.5±51.8 (nVNS) versus 12.8±45.5 (sham), p=0.03 **eCH:** -14.4±59.5 (nVNS) versus 16.3±51.5 (sham), p=0.03 **cCH:** 1.0±28.6 (nVNS) verus 5.4±29.2 (sham), p=0.69 *Rescue medication use in the first 60 mins after treatment initiation* **All CH:** 38.3% (nVNS) versus 50.7% (sham), p=0.15 **eCH**: 42.1% (nVNS) versus	29% (nVNS) versus 13% (sham); p=0.11 *Pain free status within 15 mins in treated attacks during the open label period* **All CH:** 14% **eCH:** 26% **cCH:** 11% *Safety and Tolerability* 40% (nVNS) and 27% (sham) experienced ≥1 AE during the double blind period 18% (nVNS) and 19% (sham) reported ≥1 ADE during the double blind period N=2 subjects reported 4 SAEs during the study none were treatment related.	maintained through the extension phase. Addition of nVNS to SoC during the extension phase did not result in a significant reduction in the use of abortive medication (∆= -3.4, 95% CI: -11.5 to 4.7) p=0.40) *Use of nVNS as abortive therapy* 93.8% (45/48) of participants in the nVNS+SoC arm acutely treated ≥1 CH with nVNS during th randomisation phase. During the extension phase 68.2% (30/44) in the nVNS+SoC arm and 83.3% (40/48) in the SoC arm treated ≥1 CH attack with nVNS		triptans but continued to use some oxygen and 9 patients reduced their use of triptans by a mean of 48%±6%. *Effects of attack frequency* There was a reported reduction in 24 hour attack frequency with prophylactic nVNS from a mean 4.5 to 2.6. *Effect on bout duration* 2 patients with eCH reported a shorenting of bout length using nVNS basaed on average duration of prior bouts.	Observed AEs included redness and muscle soreness at the treatment site. Benefits reported by patients during evaluation included: • Decreased interictal headache pain • No longer being housebound • Ability to return to work or school • Improved sleep • Decreased absenteeism • Avoidance of surgery intended to treat CH • Improved quality of life	

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
	48.9% (sham), p=0.53 **cCH:** 31.8% (nVNS) versus 53.9 (sham), p=0.13		*Quality of Life* *EQ-5D-3L changes from baseline* In the mITT population (baseline to randomised), changes from baseline were significantly improved for nVNS+SoC compared with SoC alone – (nVNS+SoC minus SoC: ∆=0.194 (95% CI 0.054-0.334), p=0.007) The change in EQ-5D-3L index score in the nVNS+SoC group was above the MID (0.074) and considered clinically meaningful. Addition of nVNS to the control group (extension phase) was associated with a clinically meaningful change				

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
			(0.078 points (95% CI -0.02 to 0.18) In the randomised phase, change from baseline VAS score was greater for nVNS+SoC (nVNS+SoC minus SoC: ∆=8.93 points (95% CI 0.47-17.39, p=0.039) Changes in mean HIT scores were greater in the nVNS+SoC group compared with SoC alone and were above the MID (-2.3 points), the absolute mean HIT scores suggest CH attacks have a substantial impact on QoL (data NR) *Safety, tolerability and perceptions* 7 individual discontinued due to				

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
			AEs; 93% (108/116) of AEs were classed as mild to moderate. 38% (18/48) in the nVNS+SoC versus 27% (13/49) in the SoC group experienced AEs in the randomised phase. 25% (12/48) in the nVNS+SoC group versus 24% (12/49) in the SoC group experienced AEs in the extension phase. Most common AEs were CH attacks, headache, nasopharyngitis, dizziness, oropharyngeal pain and neck pain. N=4 (2 per group) reported SAEs none of which were considered related to the nVNS device.				

Study name	Silberstein et al (2016)	Goadsby et al (2018)	Gaul et al (2015)	Gaul et al (2017)	Nesbitt et al (2015)	Marin et al (2018)	Trimboli at al (2018)
			N=15 device related AEs were reported by 11 individuals during the randomised phase (87% (n=13) were mild to moderate) N=7 participants who began nVNS therapy reported device related AEs in the extension phase. 65% of participants (62/96) indicated they would recommend the nVNS device. >75% indicated the device was easy to use and >50% reported some degree of satisfaction with nVNS.				

Abbreviations:

AE: Adverse Events; CH: Cluster Headache; cCH: Chronic Cluster Headache; CM: Chronic Migraine; eCH: Episodic Cluster Headache; EHF: European Headache Federation; HIT: Headache Impact Test; ICHD: International Classification of Headache Disorders; ITT: Intent to Treat; mITT: Modified Intent to Treat; NR: Not Reported; nVNS: Non-invasive Vagus Nerve Stimulation; SAE: Serious Adverse Events; SADE: Serious Adverse Device Events; SoC: Standard of Care; TAC: Chronic Trigeminal Autonomic Migraine

DeCoo et al (2019

Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Pooled Analysis Intervention: nVNS+SoC Comparator: Sham+SoC **Statistical Analysis** Logistic regression models to estimate odds ratios & 95% CI Site included as a covariate in analysis Generalised linear mixed-effects regression models (with logit link and binomial response distribution) Fixed effects meta-analysis models were used to	N=225 Patients with Cluster Headache from 2 randomised controlled trials (ACT1 n=133 and ACT2 n=92), (Intent to treat populations, defined as all randomly assigned subjects who treated ≥1 CH attack)Randomized phase only. Episodic Cluster Headache n=112 Chronic Cluster Headache n=113 **Inclusion/Exclusion** Full inclusion and exclusion criteria for the individual trials can be found in Silberstein et al (2016), ACT 1 and Goadsby et al (2018). ACT 2.	ACT 1 Primary Outcome: Response (defined as proportion of patients achieving a pain intensity score of 0 or 1 at 15 minutes after treatment initiation for first attack. (Rescue medication use within 60 minutes was considered a treatment failure) ACT 2 Primary Outcome: Proportion of all treated attacks achieving pain free status within 15 minutes after treatment initiation. Proportion of patients with responder status at 15 minutes for ≥50% of attacks	***Response (pain score 0-1) at 15 minutes*** *All Cluster Headaches* nVNS: 32% Sham: 21% Absolute Difference: 11% OR=1.72 (0.93-3.17), p=0.08 *Episodic Cluster Headaches* nVNS 39% Sham 12% Absolute Difference 27% (p=0.01) OR=4.67 (1.77-12.32), p<0.01 *Chronic Cluster Headaches* nVNS: 25% Sham: 30% Absolute Difference -5% OR=0.74 (0.32-1.72), p=0.48 ***Proportion of attacks pain free at 15 minutes***	***ACT 1 Withdrawals*** *from* Silberstein et al (2016), nVNS +SoC 14 discontinuations for randomized phase 3 Nonadherence 8 No CH/CH ended 2 Loss to follow up 1 other ***ACT 2 Withdrawals*** *from Goadsby et al. (2018)* nVNS +SoC double blind phase 2 Missing diary 1 Protocol Violation 2 other	Results are for the pooled analysis only There are results for the ACT 1 an ACT 2 trials which have not been reported in the respective trial publications as they were not outcomes in the trials. Results for the ACT1 and ACT2 studies have not been reported here as this publication is a pooled analysis therefore only the pooled results are of relevance. The authors state that this is a meta-analysis however the EAC disagree. A fixed effects model was used to pool data however no information on study weighting or heterogeneity analysis was detailed. The authors state “Our analysis represents the first adequately powered analysis to assess the differential

Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
estimate the pooled effects of nVNS treatment	**Baseline Demographics** See Silberstein et al (2016) for ACT 1 demographics and Goadsby (2018) for ACT 2 demogrpahics		*All Cluster headaches* nVNS:13.2% Sham: 8.7% Absolute Difference: 4.5% (p=0.13) *Episodic Cluster Headaches* nVNS: 24.1% Sham: 7.3% Absolute Difference: 16.8% (p<0.01) There is a discrepancy between the text and tables (text reports an absolute difference of 22%) *Chronic Cluster Headaches* nVNS: 6.8% Sham: 10.9% Absolute Difference: -4.1 (p=0.28) ***Pain free at 15 minutes in ≥50% of attacks*** *All Cluster headaches* nVNS: 14% Sham: 7%		effect of a specific treatment between the two forms of cluster headache". The EAC disagree as a) this is a post-hoc pooled analysis of two randomised trials and b) there are no details of any power calculation to suggest numbers needed for subgroup analysis. The EAC consider that even had a power calculation been included, because this is a post-hoc analysis and not a meta-analysis or a randomised trial, it is not accurate to say this is adequately powered for a sub-group analysis.

Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
			Absolute Difference 7% OR=2.16 (0.88-5.33), p=0.09 *Episodic Cluster Headaches* nVNS: 21% Sham: 3% Absolute Difference: 18% OR=7.68 (1.59-37.10), p=0.01 *Chronic Cluster Headaches* nVNS: 7% Sham: 11% Absolute Difference -4% OR=0.67 (0.18-2.51), p=0.55 ***Pain free or mild pain at 15 mins in ≥50% of treated attacks*** *All Cluster Headaches* nVNS: 32% Sham: 18% Absolute Difference: 14% OR=2.17 (1.17-4.04) p=0.01		

Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
			Episodic Cluster Headaches nVNS: 42% Sham: 15% Absolute Difference: 27% OR=4.12 (1.66-10.21), p<0.01 *Chronic Cluster Headaches* nVNS: 23% Sham: 21% Absolute Difference: 2% OR=1.14 (0.47-2.78), p=0.77		

Appendix C: GRADE Assessment for included studies (key outcomes only)

Question: GammaCore compared to Standard of Care for Cluster Headaches
Setting: Cluster Headache Population

Certainty assessment							Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Absolute (95% CI)	
Reduction in Pain Intensity (follow up: range 2 weeks to 4 weeks; assessed with: Patient Reported Pain Score)									
2 [1,2]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	not pooled	see comment	⊕⊕◯◯ LOW
Reduction in Attack Frequency (assessed with: Different methods used to measure outcome but all based on patient reported data)									
5 [3,4,5,6,7]	observational studies	serious [c]	serious [d]	serious [e]	serious [f]	none	not pooled	see comment	⊕◯◯◯ VERY LOW
Pain free at 15 minutes for >=50% of treated attacks									
2 [1,2]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	not pooled	see comment	⊕⊕◯◯ LOW
Quality of Life (assessed with: EQ5D and HIT (Headache Impact Test))									
1 [3]	randomised trials	not serious	not serious	serious [g]	not serious	none	single study		⊕⊕⊕◯ MODERATE

CI: Confidence interval

Explanations

a. Studies were not in treatment refractory patients
b. Subgroup analysis was carried out to evaluate response rates in episodic and chronic cluster headaches however the studies were not powered for subgroup analysis.
c. One study was an open label randomised trial and 4 studies were cohort studies. Reduction in attack frequency was measured in different ways in each study.
d. One study reported no benefit of using GammaCore whereas the other 4 studies reported a reduction in attack frequency.
e. Two studies were in treatment refractory patient while the remaining three were not
f. Small sample sizes, patient reported outcomes and no blinding
g. Study was not in treatment refractory patients

References

1. Silberstein,et. al. 2016.
2. Goadsby,et. al. 2018.
3. Gaul et. al. 2016.
4. Gaul,et. al. 2017.
5. Nesbitt et. al. 2015.
6. Marin,et. al. 2018.
7. Trimboli,et. al. 2018.

Appendix D Quality Assessments for Published Studies

de Coo, I. F. et al. (2019) doi: 10.1177/0333102419856607.

is a Critically Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? **RCT**	No
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? **RCT**	No

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.
https://amstar.ca/Amstar_Checklist.php

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CASP Checklist: 11 questions to help you make sense of a Randomised Controlled Trial

Paper for appraisal and reference: **SILBERSTEIN et al (2016)**

Section A: Are the results of the trial valid?

1. Did the trial address a clearly focused issue?

Yes ✔
Can't Tell
No

HINT: An issue can be 'focused' In terms of
- the population studied
- the intervention given
- the comparator given
- the outcomes considered

Comments: The trial was designed to add non-invasive vagus nerve stimulation to the care pathway as a treatment option before invasive nerve stimulation while still leaving patients free to use other treatment options such as triptans or oxygen as per current standard of care.

2. Was the assignment of patients to treatments randomised?

Yes ✔
Can't Tell
No

HINT: Consider
- how this was carried out
- was the allocation sequence concealed from researchers and patients

Comments: Allocation and Concealment

Randomisation was 1:1 variable block design, stratified by site

Devices were not outwardly identifiable as active or sham and allocation was done by a trained third party according to the randomisation scheme.

3. Were all of the patients who entered the trial properly accounted for at its conclusion?

Yes ✔
Can't Tell
No

HINT: Consider
- was the trial stopped early

• were patients analysed in the groups to w h ich they were randomised

Comments: Patient flow chart detailed recruitment, loss to follow-up and participant retention at each stage of the study.

Of the 150 patients enrolled, 128 went on to take part in the open label phase of the study (n=104 in the intent to treat population).

Analysis of the primary outcome was on an intent to treat basis

Is it worth continuing?

4. Were patients, health workers and study personnel 'blind' to treatment?

Yes ✔
Can't Tell
No

Comments: Patients, study co-ordinators and investigators were blinded to treatment.

Patients were given a blinding questionnaire the results of which indicated that a considerable proportion of patients correctly guessed their treatment allocation beyond chance after first treatment. At the end of the double-blind period, a blinding estimate of 0.1 (95% CI -0.08-0.28) was achieved for the nVNS group and -0.11 (95% CI, -0.28 - 0.06) for the Sham group (Bang Index)

5. Were the groups similar at the start of the trial

Yes ✔
Can't Tell
No

HINT: Consider
• other factors that might affect the outcome, such as; age, sex, social class

Comments: Baseline demographic data for each arm were detailed in the publication. A greater proportion of nVNS patients were experiencing longer length CH attacks, 34% more differences in medication

6. Aside from the experimental intervention, were the groups treated equally?

Yes ✔
Can't Tell
No

Comments: Patients were able to access a range of prophylactic and/or abortive treatments in each arm such as triptans or oxygen

Patients were free to change treatment groups during the open label phase

Section B: What are the results?

7. How large was the treatment effect?

HINT: Consider
- what outcomes were measured
- Is the primary outcome clearly specified
- what results were found for each outcome

Comments: The primary outcome was clearly defined and a clear definition for treatment failure was provided.

There was a treatment effect which was statistically significant when considering the episodic cluster headaches.

8. How precise was the estimate of the treatment effect?

HINT: Consider
- what are the confidence limits

Comments: Analysis was conducted on the Intent to Treat population and reported for the 4 week double blind phase of the study.

It should be noted that outcomes were measured using patient reported measures of response and therefore may be subject to a degree of bias.
Treatment compliance with nVNS was not reported/Assessed

Section C: Will the results help locally?

9. Can the results be applied to the local population, or in your context?

Yes	✔
Can't Tell	
No	

HINT: Consider whether
- the patients covered by the trial are similar enough to the patients to whom you will apply this
- how they differ

Comments: The population was a cluster headache population. Treatment options for cluster headache are limited. Although conducted in the USA, alternative treatment options are the same as in the UK therefore the results are likely to be generalisable to the UK cluster headache population.

10. Were all clinically important outcomes considered?

Yes	✔
Can't Tell	
No	

HINT: Consider whether
- there is other information you would like to have seen
- if not, does this affect the decision

Comments:

11. Are the benefits worth the harms and costs?

Yes	
Can't Tell	✔
No	

HINT: Consider

- even if this is not addressed by the trial, what do you think?

Comments: There were no reported serious device related adverse events and the study reported a clinical benefit for patients using the device however the trial did not include any cost analysis.

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CASP Checklist: 11 questions to help you make sense of a Randomised Controlled Trial

Paper for appraisal and reference: **GOADSBY et al (2018)**

Section A: Are the results of the trial valid?

1. Did the trial address a clearly focused issue?

Yes	✔
Can't Tell	
No	

HINT: An issue can be 'focused' In terms of
- the population studied
- the intervention given
- the comparator given
- the outcomes considered

Comments: The trial was designed to add non-invasive vagus nerve stimulation to the care pathway as a treatment option before invasive nerve stimulation while still leaving patients free to use other treatment options such as triptans or oxygen as per current standard of care.

2. Was the assignment of patients to treatments randomised?

Yes	✔
Can't Tell	
No	

HINT: Consider
- how this was carried out
- was the allocation sequence concealed from researchers and patients

Comments: Allocation and Concealment, no details as to how randomisation sequence generated

Randomisation was 1:1, standard design with block size of 4 using sealed envelopes.

Unblinded trainers provided device (active or sham) to patients as appropriate

3. Were all of the patients who entered the trial

properly accounted for at its conclusion?

Yes ✔
Can't Tell
No

HINT: Consider
- was the trial stopped early
- were patients analysed in the groups to which they were randomised

Comments: Patient flow chart detailed recruitment, loss to follow-up and participant retention at each stage of the study.

N=102 patients were randomised to the double blind phase and n=58 carried on into the open label phase.

Analysis is on an intent to treat basis for the primary outcome.

Is it worth continuing?

4. Were patients, health workers and study personnel 'blind' to treatment?

Yes ✔
Can't Tell
No

Comments: Patients, study coordinators and investigators were blinded to treatment. Blinding assessments indicated that a similar proportion of participants in the nVNS and Sham arms correctly guessed their treatment allocation (30% versus 39% respectively).

5. Were the groups similar at the start of the trial

Yes ✔
Can't Tell
No

HINT: Consider
- other factors that might affect the outcome, such as; age, sex, social class

Comments: Baseline demographic data for each arm were detailed in the publication.

6. Aside from the experimental intervention, were the groups treated equally?

Yes ✔
Can't Tell

No

Comments: Patients were able to access a range of prophylactic and/or abortive treatments in each arm such as triptans or oxygen

Patients were free to change treatment groups during the open label phase

Section B: What are the results?

7. How large was the treatment effect?

HINT: Consider
- what outcomes were measured
- Is the primary outcome clearly specified
- what results were found for each outcome

Comments: There was a statistically significant treatment effect when considering episodic cluster headaches alone

8. How precise was the estimate of the treatment effect?

HINT: Consider
- what are the confidence limits

Comments: Double blind period was 2 weeks long, it is unclear whether this is a sufficient length of time to assess impact on episodic cluster headaches, although this may be appropriately accounted for in the exclusion criteria (Patients with eCH were excluded if not having an active bout at the time of screening).
Outcomes were patient reported
Treatment compliance with nVNS was not reported/assessed

Section C: Will the results help locally?

9. Can the results be applied to the local population, or in your context?

Yes	✔
Can't Tell	
No	

HINT: Consider whether
- the patients covered by the trial are similar enough to the patients to whom you will apply this
- how they differ

Comments: Patients were recruited from a number of European centres and the population was a cluster headache population. Alternative treatment options are the same as in the UK therefore the results are likely to be generalisable to the UK cluster headache population.

10. Were all clinically important outcomes considered?

Yes ✔
Can't Tell
No

HINT: Consider whether
- there is other information you would like to have seen
- if not, does this affect the decision

Comments:

11. Are the benefits worth the harms and costs?

Yes
Can't Tell ✔
No

HINT: Consider
- even if this is not addressed by the trial, what do you think?

Comments: There were no reported serious device related adverse events and the study reported a clinical benefit for patients using the device however the trial did not include any cost analysis.

CASP Appraisals for Cohort Studies

	Gaul et al 2017	**Nesbitt et al 2015**	**Marin et al 2018**	**Trimboli et al 2018**
Did the study address a clearly focused question	Yes	Yes	Yes	Yes
	This was a post-hoc analysis of a randomised trial population looking at the results over time	Study investigated the usefulness of nVNS device in patients with cluster headaches in a UK setting	to explore early clinical experience with nVNS used acutely and/or preventatively	Assessed whether nVNS has a role in the cluster headache treatment pathway
Was the cohort recruited in an acceptable way	Yes	Yes	Yes	No
	Cohort comprised of the population of randomised trial participants which was representative of a cluster headache population. 97 patients were randomised.	Patients being treated with nVNS at a tertiary headache centre in the UK.	Patients being treated for cluster headaches at 10 clinical centres in the UK There is a possible overlap with patients in another UK study (Nesbitt et al, 2015)	Consecutive, medically refractory, headache patients at a UK headache centre. Study included only 12 patients with chronic cluster headache and also included patients with chronic migraine and other headache types.
Was exposure accurately measured to minimise bias	Yes	Yes	Yes	Yes
	Cluster headache was defined according to standard international definitions	Yes, patients were diagnosed with cluster headache (chronic or episodic) using standard international definitions and were being treated at a dedicated headache centre	Participants were diagnosed with and being treated for cluster headaches (chronic or episodic) using standard international definitions	Cluster headache defined according to standard international criteria
Was the outcome accurately measured to minimise bias	No	Can't Tell	Can't Tell	Can't Tell
	The trial was open label, participants were aware of their treatment protocol. No sham device was used in the comparison group. Outcome reporting may be subject to bias as the outcomes are reported by the participants	Outcomes are patient reported (in a diary) No details given on how treatment compliance with nVNS was recorded. It is a handheld device which is taken home by the patient.	Outcomes are patient reported No details given on how treatment compliance with nVNS was recorded.	Patient reported outcomes An attempt was made to measure treatment compliance but this was largely an estimate.

	themselves and may therefore be somewhat subjective. The outcomes reported were not pre-specified in the clinical study protocol. Treatment compliance with nVNS was not measured.			
Have the authors identified all important confounders?	No	Can't Tell	Can't Tell	No
	No mention of possible confounding as this study was reported as an extension of a trial and baseline characteristics had been assessed	No comparator. Baseline demographics of the cohort were reported and seem broadly in line with those reported in other studies. Authors mention placebo effect as a possible confounder	No comparator. Baseline demographics of the cohort were reported and unlike other studies, this one has a higher proportion of females (63%) which is not reflective of the prevalence of cluster headaches in the general population.	No comparator at baseline; minimal cohort demographic details provided.
Have the taken account of confounding factors in the design and/or analysis?	Can't Tell	No	No	Yes
	Study cohort was a randomised trial population in which the baseline characteristics had been assessed and the two groups found to be similar.	Authors mention that it would be hard to reconcile the treatment effect of nVNS as placebo effect when considering drug-refractory patients but the study was not specifically designed to take account of possible confounders.	The authors acknowledge the higher proportion of females in the discussion and hypothesise that it is due to the fact that females are more likely to suffer co-morbidities such as major depression and migraine and may be more concerned about the teratogenicity associated with some medications.	Descriptive results due to the small number of cluster headache patients but some attempt made in the analysis to address possible reasons for reduction in sumatripan use which were independent of the device
Was follow up of subject complete?	Yes	Can't Tell	Can't Tell	Yes
Was follow-up long enough?	Yes	Yes	Yes	Yes
	Response rates were assessed in terms of response as soon as 15 minutes after treatment. For	Subjects were followed up for 1 year however full details of the follow-up methods/schedules	No details were given on the follow-up protocol other than to say the evaluation period was	Follow-up was at 3 months which given the nature of the condition is likely to be enough

	chronic headaches, long-term follow-up may be useful to determine whether nVNS continues to work for patients.	are not provided although based on the results it appears that follow-up happened at at least a 26 week and 52 week time point.	3-6 months. Given the nature of the condition, this is likely to be long enough to observe a treatment effect.	time to observe any treatment effect.
What are the results of the study	Mean weekly attack frequency was significantly lower with nVNS+SoC compared with SoC alone and a significantly higher proportion of patients in the nVNS+SoC group had attack frequency reductions from baseline compared with SoC alone.	15 patients reported an overall improvement in their condition when using nVNS preventatively. Patients reported that nVNS aborted attacks in an average of 11mins A number of patients reported being able to stop or reduce their use of triptans or oxygen Mean attack frequency was reduced from 4.5 to 2.6 attacks/24 hour period with prophylactive nVNS	Mean attack frequency reduced from 26.6 attacks/week with standard care alone to 9.6 attacks/week with standard care + nVNS. 3 patients experienced no attacks during their nVNS evaluation period Mean attack duration reduced from 51.9 mins to 29.4 mins with nVNS and mean attack severity decreased from 7.8 with standard care to 6.0 with standard care + nVNS	1 patients reported a >=30% reduction in weekly cluster headache frequency and a reduction in oxygen use; 2 patients reported a slight improvement from baseline; 3 patients reported no change and 6 patients reported a worsening in weekly frequency
How precise are the results?	Unclear, analysis used a modified Intent to Treat population which included participants with measurable observations across study phases being compared. Outcomes were recorded by patients and may be subject to a degree of bias	Unclear There is no comparator group and the sample size in the study is small (n=25) Changes in outcomes are compared with patient reported baselines which may be subject to bias	Unclear There is no comparator group and the sample size in the study is small (n=30) Changes in outcomes are compared with patient reported baselines which may be subject to bias	Unclear There is no comparator group and the sample size in the study is small (n=12), in addition the cluster headache population is a subgroup population. Changes in outcomes are compared with patient reported baselines which may be subject to bias
Do you believe the results	Can't tell	Can't Tell	Can't Tell	Can't Tell
	Results are reported by patients themselves and therefore may reflect a true effect however the trial was an open label trial	The results show some clinical benefit of nVNS which is broadly in line with the results of the randomised trials however this is	The results show some clinical benefit of nVNS which is broadly in line with the results of the randomised trials	The results show limited benefit of nVNS and 50% of the cluster headache population reported a

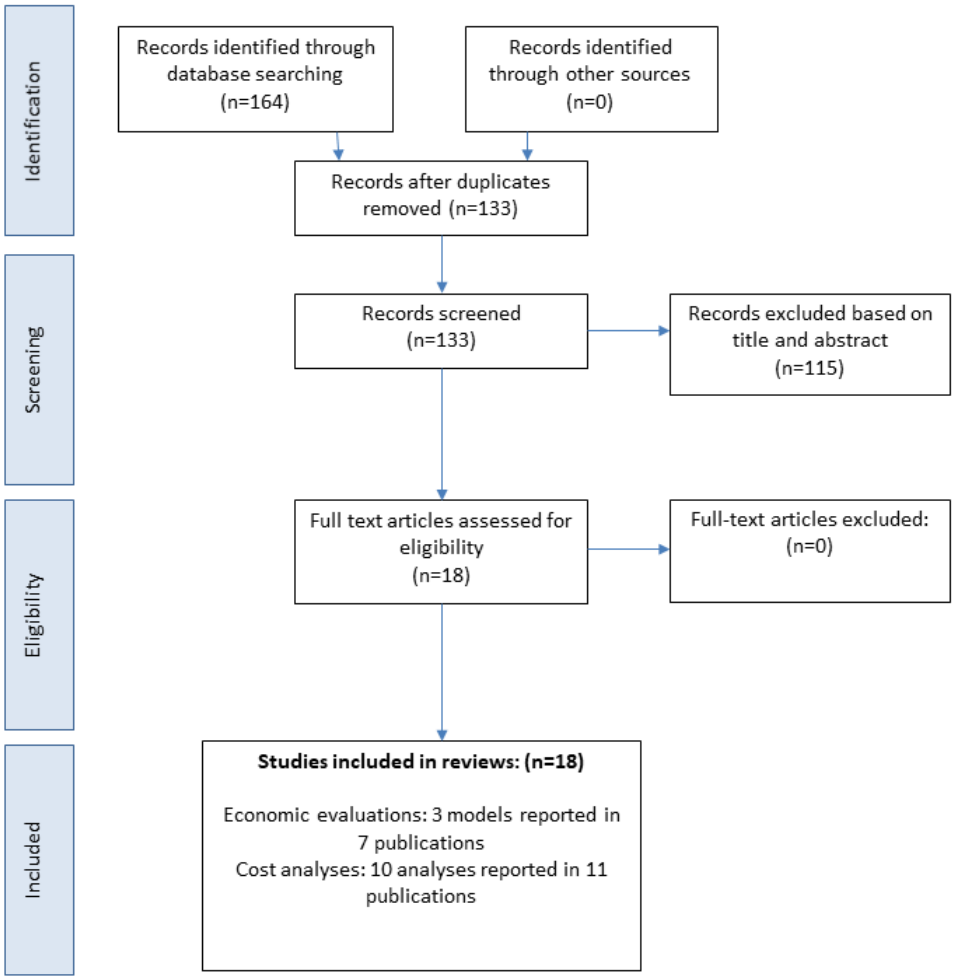
	therefore the possible placebo effect cannot be ruled out. Analysis was conducted in a modified ITT population and there may be a risk of bias in that some patients will be more motivated to report their outcomes and carry on in the study past the randomisation phase. The population is a chronic cluster headache population and the results show a significant clinical benefit of nVNS whereas two randomised trials (Siberstein (2016) and Goadsby (2018) did not show a significant effect in the chronic cluster headache population.	a small study which might be at high risk of bias.	however this is a small study which might be at high risk of bias.	worsening of their condition. This is not in line with the results of other studies.
Can the results be applied to the local population	Yes	Yes	Can't Tell	Can't Tell
	Chronic cluster headache population in the study thought to be representative of the more general chronic cluster headache population. Study recruited patients from the UK as well as 9 other European countries	This study is likely to be reflective of the wider cluster headache population in the UK	This study may not be reflective of the wider UK cluster headache population in that it is 63% female.	This study may not be reflective of the wider UK cluster headache population and may be at high risk of bias given the small sample size
Do the results fit with other available evidence?	Can't tell	Yes	Yes	No
	The population is a chronic cluster headache population and the results show a significant clinical benefit of nVNS whereas two randomised trials (Siberstein (2016) and Goadsby (2018) did not show a significant effect in	This study shows some clinical benefit of nVNS in the management of Cluster Headaches	This study shows some clinical benefit of nVNS in the management of Cluster Headaches	The results show limited benefit of nVNS and 50% of the cluster headache population reported a worsening of their condition. This is not in line with the results of other studies.

	the chronic cluster headache population.			
What are the implications of this study for practice?	Can't tell	Can't Tell	Can't Tell	Can't Tell
	The results show a possible clinical benefit for patients with chronic cluster headaches and the population is relevant to the UK. There were no adverse device events recorded and device discontinuation was similar in both groups. No cost analysis	The results show a possible clinical benefit for patients with chronic cluster headaches and the population is relevant to the UK. There were no adverse device events recorded and device discontinuation was similar in both groups. No cost analysis	The results show a possible clinical benefit for patients with chronic cluster headaches and the population is relevant to the UK. There were no adverse device events recorded and device discontinuation was similar in both groups. No cost analysis	This study showed very limited clinical benefit and some patients reported a worsening of their condition. No serious device related adverse events were reported No cost analysis

Appendix E: Company search strategy for clinical evidence

The company conducted a separate search for economic evidence which included a search of the following databases: Medline and Medline In-Process databases were searched through PubMed.gov using the Entrez service provider; Embase and Embase Alert via Proquest; DARE, NHS EED and HTA via CRD; Heoro.com database. Search terms included terms to describe 'cluster headaches' and economic studies.

Company's PRISMA diagram for Economic Evidence



EAC search strategy for economic evidence

The EAC designed one strategy to identify both published clinical evidence, evidence reporting adverse events and economic evidence, details provided in appendix A. Citation tracking of the EAC's included economic papers (Jenks et al. 2016, Morris et al. 2017, Mwamburi et al. 2017a) was conducted

in Google Scholar. The included papers of an economic review (Mwamburi et al. 2017b) were also checked for relevance.

Appendix F: Excluded Cost Analysis Studies

Study	Methods	Population	Setting
Choong 2018	Database Analysis of direct costs	Cluster Headache	USA
Polson 2017	Database Analysis of direct costs	Cluster Headache	USA
Ford 2018	Database Analysis of direct costs Also reported indirect costs	Cluster Headache	USA
Gaul 2011	Database analysis of direct and indirect costs	Cluster Headaches (episodic and chronic)	Germany
Pietzsch 2018	Costs savings and reduction in medication use following SPG stimulator implantation	Chronic cluster headaches	Germany
Pietzsch 2017 (conference abstract)	Costs savings and reduction in medication use following SPG stimulator implantation	Chronic cluster headaches	Germany
O'Brien 2017	Costs of different types of oxygen cylinders	Chronic cluster headache	USA
Mueller 2013	Costs associated with occipital nerve stimulation	Chronic cluster headache	Germany
Gaul & Muller 2013	Costs associated with occipital nerve stimulation	Chronic cluster headache	Germany

Thavaneswaran 2016	Costs associated with occipital nerve stimulation	Chronic cluster headache	UK
Leone 2009	Reduction in medication costs after hypothalamic stimulation	Chronic Cluster headache	Italy

Appendix G Model Testing

Test Scenario	Gamma-Core	Comparator	Difference	Comment
Base Case	£3,448.45	£3,898.86	-£450.41	
Set gammaCore cost to 0	£2,931.27	£3,898.86	-£967.60	Comparator unchanged, intervention cheaper
Set all medication and gammacore to £0	£0.00	£0.00	£0.00	As expected
Set just medications to £0	£517.8	£0	£517.8	As expected
Set gammcore cost to £3000 per 3 months	£5,413.73	£3,898.86	£1,514.87	Becomes cost incurring, comparator unchanged
Probability of discontinued response per month for initial responders set to 0%	£3,413.21	£3,898.86	-£485.65	Gamma core initial responsers stays static at 40%. gammaCore arm costs decrease, as decrease in meds >cost of gammaCore
Probability of discontinued response per month for initial responders set to 50%	£3,469.97	£3,898.86	-£428.90	Initial responders of 40% then changes to 20%. Gamma core cost slight increase, as less responders
Probability of discontinued response per month for initial responders set to 100%	£3,526.72	£3,898.86	-£372.14	None getting gammacore after cycle 2. Cost saving driven by small number of responders in 1st month plus non-responders in 1st 3 months who still experience a reduction in other drug use. After 1st 3 months costs are the same in both arms.
Double time horizon	£7,659.12	£8,142.27	-£483.15	As expected, increase costs, but little difference in incremental change, as most of the impact is in first 3 months. In the base case after the 3rd month the cost saving is only £2 per month.
Reduce time horizon to 3 months	£857.27	£1,287.54	-£430.27	Lower costs, and very slightly lower cost saving - most

Test Scenario	Gamma-Core	Comparator	Difference	Comment
				difference occurs in first 3 months.
Oxygen cost £0	£3,300.90	£3,710.37	-£409.47	lower costs for both arms, difference decreases
Zulmitripan costs £0	£3,242.12	£3,694.02	-£451.90	lower costs for both arms, difference decreases
Sumatriptan (all sorts) cost £0	£871.06	£393.34	£477.72	Incurrs large cost. Demonstrates the extent to which the model is driven by Sumatriptan costs and resource use.
Set both markov traces to have all patients in non-responder arm.	£3,567.05	£3,916.99	-£349.94	Still cost saving, although reduced. Both are in non-responder group, but 1st 3 months gammaCore non-responders have reduced medication use.
As above, but no allowance for reduced medications in gammaCore non-responders (months 1-3)	£3,916.99	£3,916.99	£0.00	Equal costs, gammaCore non-responders costed in the same way as standard care
Add initial cost of primary care consultation (1.9*13) with nurse	£3,473.15	£3,898.86	£425.72.	(cost is PRSSRU, primary care GP nurse, 20 min at £36 per hour)
In addition to cost of initial consultation add outpatient appointment every 3 months	£3,738.14	£3,898.86	-£160.73	(cost used is £145 I91 Total pain management outpatients consultation, Ref Costs 2017-18)

Appendix G PREVA Inclusion criteria

The subjects had to meet all of the following criteria to be eligible to enter the investigation (formatting as submitted):

1. Signed Informed Consent Form
2. Subjects between the age of 18-70, both genders
3. Subjects diagnosed with cluster headache for at least 1 year, without remission periods or with remission periods lasting <1 month, in accordance with the ICHD-II classification criteria (2ndEd):

a. At least 5 attacks fulfilling the following criteria:

i. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated

ii. Headache is accompanied by at least 1 of the following:

1. Ipsilateral conjunctival injection and/or lacrimation
2. Ipsilateral nasal congestion and/or rhinorrhoea
3. Ipsilateral eyelid oedema
4. Ipsilateral forehead and facial sweating
5. Ipsilateral miosis and/or ptosis
6. A sense of restlessness or agitation

iii. Attacks have a frequency from 1 every other day to 8 per day and are not attributed to another disorder

iv. Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month

4. Had minimum mean attack frequency of 4 CH attacks per week
5. Was able to distinguish CH from other headaches (i.e. tension-type headaches)
6. Was capable of completing headache pain self-assessments
7. Agreed to use the gammaCore® device as intended and follow all of the requirements of the study, including follow-up visit requirements
8. Was willing to keep all concomitant medication stable during the entire study period
9. Women of child-bearing potential used 2 methods of contraceptive i.e. hormones and condom

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

gammaCore for cluster headache

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from scope

1 The technology

gammaCore (electroCore) is a handheld, patient-controlled, non-invasive vagus nerve stimulator used for treating and preventing cluster headaches. The patient holds the device to their neck (over the cervical branch of the vagus nerve) and uses it to deliver a small electric current for about 2 minutes. The aim of treatment is to modify pain signals by stimulating the vagus nerve through the skin of the neck. gammaCore can be used acutely when the person feels a cluster headache beginning or daily to help prevent cluster headaches. The device is small and portable and, after brief training, is designed to be used anywhere that is convenient.

2 Proposed use of the technology

2.1 Disease or condition

Cluster headaches are excruciating attacks of pain in one side of the head, often felt around the eye. An attack may last between 15 minutes and 3 hours and can typically occur between 1 and 8 times a day. Cluster headaches may be classed as episodic or chronic, people with episodic cluster headache will have extended pain free intervals whereas those classed as having chronic cluster headaches do not.

Expert advice has stated that many people with cluster headache do not get enough pain relief with current treatment options, which are often limited by side effects and contraindications.

2.2 Patient group

gammaCore is intended for use by people with cluster headache for whom standard treatment has been unsuccessful or in people who cannot have other prescribed treatments. If used, it is most likely to be an option before more invasive procedures or treatments with serious side effects are considered.

Cluster headache is a rare condition experienced by around 0.1% of people in the UK (electroCore company submission, 2019). Cluster headaches are

more common in men and tend to start when a person is in their 30s or 40s. The company estimate that standard care will not work or be unsuitable for about 5% of people with cluster headache. Expert advice suggests that 5% may be an underestimate because some people only receive a partial benefit from standard care treatments.

2.3 Current management

NICE's clinical guideline on headache states that oxygen and/or subcutaneous or nasal spray triptan should be offered for acute treatment of cluster headache. The guideline states that paracetamol, NSAIDS, opioids, ergots or oral triptans should not be offered for the acute treatment of cluster headache as they are not effective.

The guideline recommends that verapamil is considered for long-term prophylaxis and that patients taking this drug receive regular electrocardiogram monitoring. Other treatments which may be offered to prevent cluster headache include oral steroids (such as prednisolone) prescribed on their own or alongside verapamil but these can only be used for a short time due to side effects. Anticonvulsants and lithium carbonate may also be offered. Lithium carbonate requires close monitoring through blood tests to avoid toxicity. The use of verapamil, anticonvulsants and lithium carbonate for cluster headache is outside their marketing authorisations.

Current NHS practice also includes offering additional or alternative treatment options when first-line treatments are ineffective or not tolerated. These include invasive treatments such as surgically implanted sphenopalatine ganglion nerve stimulators, deep brain stimulation (which requires neurosurgery) and occipital nerve block injections. Intravenous dihydroergotamine (unlicensed) is available at specialist centres to a small number of people, in whom verapamil and anticonvulsants are ineffective. This treatment requires a 5-day inpatient stay.

NICE interventional procedures guidance on transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (2016)

recommends that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

2.4 Proposed management with new technology

gammaCore is intended for use by people with cluster headache for whom standard treatment has been unsuccessful or in people who cannot have other prescribed treatments. If used, it is most likely to be an option before more invasive procedures or treatments with serious side effects are considered.

3 Company claimed benefits and the decision problem

These are described in the scope here (link to Appendix E).

Decision problem	Variation proposed by company	EAC view of the variation
Intervention – gammaCore	Intervention – gammaCore all versions of the device including gammaCore Sapphire (most recent version).	The EAC consider the devices to be essentially the same for the purposes of the evaluation.
Comparator – • Subcutaneous or nasal spray triptan therapy (acute) • Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute) • Verapamil (preventative) • Sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache) • Occipital nerve block (preventative).	No variation.	Although the company submission matches the decision problem as laid out in the scope, the EAC notes that some of these are not comparators in the true sense as the clinical pathway states that gammaCore will be used when these treatments are ineffective for patients (or instead of if contraindicated).
Cost analysis	The submitted economic model considered chronic cluster headache only.	The rationale given was that UK based evidence suggests only small

		numbers of patients with episodic cluster headache are likely to be offered gammaCore in the UK. The following were not included in the model as comparators: Verapamil (preventative), sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache), occipital nerve block (preventative)

4 The evidence

4.1 Summary of evidence of clinical benefit

The company submission presented 6 published studies and 2 conference abstracts. The published studies comprised 3 randomised trials (Silberstein et al. 2016, Goadsby et al. 2018, and Gaul et al. 2016), 1 post hoc analysis of a randomised trial (Gaul et al. 2017), and 3 non-comparative cohort studies (Trimboli et al. 2018, Nesbitt et al. 2015, and Marin et al. 2018). The 2 conference abstracts described a pooled analysis (deCoo et al. 2017) and a post hoc analysis of a randomised trial (Gaul et al. 2018).

The EAC agreed with the studies selected by the company and did not identify any additional studies. The rationale for the study selection is described in section 3.3 of the assessment report.

The EAC noted that the evidence for gammaCore is comprised of a small number of studies which includes non-comparative and observational studies. However, the EAC understood that with the very low prevalence of cluster headaches it is unlikely that large randomised trials would be possible. The studies had short follow-up times so there is no evidence for the long-term benefits of using gammaCore.

The EAC also noted that there were differences in the way gammaCore was used in the studies. In Gaul et al. (2016) gammaCore was used in addition to

standard care for prevention and acute treatment of cluster headache. In the ACT1 and ACT2 studies (Silberstein et al. 2016 and Goadsby et al. 2018) gammaCore was used as an acute treatment for cluster headache in addition to standard of care, the use of gammaCore to prevent cluster headaches was not considered. Two cohort studies (Marin et al. 2018 and Trimboli et al. 2018) reported on the use of gammaCore (both preventative and acute) in people who are classed as treatment refractory to standard of care.

Two of the randomised trials (ACT 1 and ACT 2) observed better responses to gammaCore from people with episodic cluster headache compared with those with chronic cluster headache. The EAC advise that these conclusions should be interpreted with caution as the studies were not powered for subgroup analysis.

The EAC concluded that the published evidence suggests that people with cluster headache may benefit from using gammaCore (either preventatively or acutely), however, the degree of benefit is not clear from the published evidence.

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Silberstein et al. (2016) Double-blind randomised control trial followed with an open label period (ACT1). Location: 20 centres in USA.	150 people with cluster headache (101 with episodic cluster headache and 49 with chronic cluster headache).	gammaCore in addition to standard care (73 people) versus sham device in addition to standard care (77 people). gammaCore protocol: 3 consecutive 2 min stimulations when pain starts. Rescue medications were permitted no sooner than 15 mins after gammaCore treatment.	Primary outcome: *Response rate* – proportion of patients with a pain intensity score of 0 or 1 at 15 mins after treatment begins. Use of rescue medication within 60 mins was considered a treatment failure. Secondary outcomes: *Sustained treatment response* – proportion of patients with a pain intensity score of 0 or 1 without rescue medication at 15–60 mins after treatment begins. CH attack) *Average of all patients' mean*	*Response rate (gammaCore versus sham)* – All cluster headache: 26.7% versus 15.1%, p=0.1. Episodic cluster headache: 34.2% versus 10.6%, p=0.008. Chronic cluster headache: 13.6% versus 23.1%, p=0.48. *Sustained treatment response (gammaCore versus sham)* – All cluster headache: 26.7% versus 12.3%, p=0.04. Episodic cluster headache: 34.2% versus 10.6%, p=0.08. Chronic cluster headache: 13.6% versus 14.5%, p=1.0. *Average of all patients' mean pain intensity at 15 mins (gammaCore versus sham)* – All cluster headache: 2.1 [95% CI, 1.8–2.3] versus 2.0 [95% CI, 1.8–2.2], p=0.4.	In the gammaCore in addition to standard care group 14 patients left the double-blind to open label phase, 3 due to non-adherence, 8 due to having no cluster headaches, 2 lost to follow up and 1 for 'other' reasons.	The study was sponsored by the company with data analysis funded by the company. One of the authors is an employee of the company.	This study only considered the use of gammaCore as an acute treatment for cluster headache. Use of gammaCore to prevent cluster headaches was not considered. Patients that took part in the study were not necessarily treatment refractory to standard of care, 68% were using standard of care treatments for cluster headache prevention at the beginning of the study. The study reports results for the double-blind randomised period only. A pooled analysis of data collected in this study is reported in the deCoco et al. (2019) conference abstract.

			pain intensity at 15 mins – mean pain intensity was calculated from up to 5 attacks per patient). Follow-up period: February 2013 to October 2014	Episodic cluster headache: 2.0 [95% CI, 1.8–2.3] versus 2.0 [95% CI, 1.8–2.3], p=1.0. Chronic cluster headache: 2.3 [95% CI, 1.9–2.6] versus 1.9 [95% CI, 1.6–2.3], p=0.2.			The study was not powered for subgroup analysis.
Goadsby et al. (2018) Double-blind randomised control trial followed with an open label period (ACT2). Location: 9 centres in 4 European countries including the UK (52 UK patients).	102 people with cluster headache (30 with episodic cluster headache and 72 with chronic cluster headache).	gammaCore in addition to standard care (50 people) versus sham device in addition to standard care (52 people). gammaCore protocol: 3 consecutive 2 min stimulations when pain starts. 3 additional stimulations were allowed if pain was not gone within 9 minutes. Rescue medications were permitted no sooner	Primary outcome: *Proportion of all treated attacks reaching pain free status within 15 mins.* Secondary outcomes: *Proportion of treated attacks per subject reaching responder status within 30 mins.* *Proportion of treated attacks per subject reaching pain free status within 30 mins.* *Mean change in pain intensity from attack onset to 15 and 30 mins.*	*Pain free status within 15 mins (gammaCore versus sham)* – All cluster headache: 14% versus 12%, p=0.71. Episodic cluster headache: 48% versus 6%, p<0.01. Chronic cluster headache: 5% versus 13%, p=0.13. *Proportion reaching responder status within 30 mins (gammaCore versus sham)* – All cluster headache: 43% versus 28%, p=0.05. Episodic cluster headache: 58% versus 28%, p=0.07. Chronic cluster headache: 37% versus 29%, p=0.34. *Proportion reaching pain free status within 30 mins (gammaCore versus sham)* – All cluster headache: 26% versus 18%, p=0.17.	In the gammaCore in addition to standard care group 5 patients left the double-blind phase, 2 due to missing diaries, 1 protocol violation and 2 due to 'other' reasons. 2 patients left the open label phase, 1 due to adverse events and 1 due to 'other' reasons. In the sham device in addition to standard care group 14 patients left the double-blind phase, 6 due to missing diaries, 2 due to no attacks treated, 2 withdrew, 2 lost to follow up and 2	The study was sponsored by the company with data analysis funded by the company. One of the authors is an employee of the company.	This study only considered the use of gammaCore as an acute treatment for cluster headache. Use of gammaCore to prevent cluster headaches was not considered. Patients that took part in the study were not necessarily treatment refractory to standard of care, 61% were using standard of care treatments for cluster headache prevention at the beginning of the study. The study reports results for the double-blind randomised period only.

		than 15 mins after gammaCore treatment.	*Patients reaching pain free status in ≥50% of treated attacks within 15 mins.* *Patients reaching responder status in ≥50% of treated attacks within 15 mins.* Follow-up period: September 2013 to October 2014.	Episodic cluster headache: 43% versus 19%, p=0.08. Chronic cluster headache: 19% versus 18%, p=0.76. *Mean change in pain intensity from attack onset to 15 and 30 mins (gammaCore versus sham)* – All cluster headache: 15 mins, -1.3 versus -0.9, p=0.06. 30 mins, -1.6 versus -1.2, p=0.07. Episodic cluster headache: 15 mins, -1.7 versus -0.6, p=0.01. 30 mins, -1.9 versus -0.8, p=0.03. Chronic cluster headache:15 mins, -1.2 versus -1.0, p=0.52. 30 mins, -1.5 versus -1.3, p=0.5. *Patients reaching pain free status in ≥50% of treated attacks within 15 mins (gammaCore versus sham)* – All cluster headache: 17% versus 7%, p=0.15. Episodic cluster headache: 36% versus 8%, p=0.16. Chronic cluster headache: 9% versus 7%, p=1.00. *Patients reaching responder status in ≥50% of treated attacks within 15*	due to adverse events. 2 patients were lost to follow-up in the open label phase.		A pooled analysis of data collected in this study is reported in the deCoco et al. (2019) conference abstract. The study was not powered for subgroup analysis and did not reach the sample size required for power of primary outcome.

				mins (gammaCore versus sham) – All cluster headache: 40% versus 14%, p<0.01. Episodic cluster headache: 64% versus 15%, p<0.01 Chronic cluster headache: 29% versus 13%, p=0.11.			
Gaul et al. (2016) Randomised, multi-centre, open label, parallel group study (PREVA). Location: 10 centres in Europe including 3 in the UK (24 UK patients).	97 people with chronic cluster headache.	gammaCore in addition to standard of care (48 people) versus standard of care only (49 people). gammaCore protocol: Mandatory prophylaxis, of 3 stimulations lasting 2 mins, 5 mins apart, twice daily. Patients also had the option of using gammaCore for acute attacks (3 stimulations at pain onset).	Primary outcome: *Reduction in the mean number of attacks per week* – reduction in number of attacks during the last two weeks of the randomised phase compared to the number of attacks during baseline. Secondary outcomes: *≥50% response rate* – Proportion of patients with ≥50% reduction in mean number of attacks per week, assessed during the last 2 weeks of	*Reduction in the mean number of attacks per week (gammaCore versus standard of care)* – -5.9 versus -2.1, mean therapeutic gain of 3.9 fewer CH attacks per week (95% CI 0.5–7.2, p=0.02) *≥50% response rate (gammaCore versus standard of care)* – 40% versus 8.3%, p<0.001. *Rescue medication use (gammaCore versus standard of care)* – 57% decrease in the gammaCore group (∆= -15 (95% CI: -22.8 to -7.2), p<0.001) versus ∆= -2 (95% CI: -9.4 to 5.4), p=0.59). *Use of gammaCore to treat acute attacks* – 93.8% of people in the gammaCore group used it to treat ≥1 acute attack during the randomisation phase.	In the gammaCore in addition to standard care group 4 patients left the randomised phase by withdrawing and 11 left the extension phase, 4 withdrew, 2 were lost to follow-up, 1 due to a protocol violation, 3 due to adverse events and 1 due to 'other' reasons. In the standard of care only group 1 patient left the randomised phase as they did not meet the inclusion/exclusion criteria and 11 left the extension phase, 4 were lost to follow-up, 1 due to a protocol	The study was funded by the company. One of the authors is an employee of the company.	In this study gammaCore was used to prevent cluster headaches in addition to standard of care treatments for cluster headache prevention. Patients were therefore not necessarily treatment refractory to standard of care, 53% were using verapamil at the beginning of the study and a smaller percentage were using other preventative treatments. Changes in abortive medication use were driven by reductions in use of sumatriptan (p=0.007) and inhaled oxygen (p=0.02). These reductions were

			randomisation and last two weeks of extension phases. *Rescue medication use.* *Use of gammaCore to treat acute attacks.* *Quality of life* – Measured using EQ-5D-3L and HIT-6 Follow-up period: October 2012 to March 2014.	*Quality of life* – EQ-5D-3L indexed score changes from baseline were significantly improved for people using gammaCore versus standard of care only (Δ=0.194 (95% CI 0.054–0.334), p=0.007), this increase is considered clinically meaningful. EQ-5D-3LVAS score change from baseline was greater for people using gammaCore versus standard of care only (Δ=8.93 points, 95% CI 0.47–17.39, p=0.039) 65% of Said they would recommend gammaCore, >75% said it was easy to use and >50% reported some degree of satisfaction with gammaCore.	violation, 2 due to adverse events and 4 due to 'other' reasons.		maintained through the extension phase. Due to the open label study design outcome assessment could not be blinded, patients self-reported outcomes. Post hoc analyses of data collected in this study are reported in Gaul et al. (2016) and in the Gaul et al. (2018) conference abstract.
Gaul et al. (2017). Post-hoc analysis of data from a randomised, multi-centre, open label, parallel group study (Gaul et al. 2016).	As Gaul et al. (2016).	As Gaul et al. (2016).	*Mean weekly attack frequency over time* *Global percentage change in weekly attack frequency* – from baseline to the end of the randomised phase	*Weekly attack frequency* – Significantly lower for people using gammaCore versus standard of care only (p<0.02) from week 2 of the randomised phase until week 3 of the extension phase. This was also significantly reduced (p<0.05) during the baseline to week 4 of the extension phase period.	As Gaul et al. (2016).	As Gaul et al. (2016).	This study is a post hoc analysis of data collected in the Gaul et al. (2016) study. The outcomes reported in this study were not included in the original study protocol for Gaul et al. (2016). The EAC have critically appraised this study

Location: 10 centres in Europe including 3 in the UK (24 UK patients).			*Response rate* – Cut-offs of ≥25%, ≥50%, ≥75% and 100% reductions from baseline in attack frequency were used to define response.	*Global mean attack frequency* – Decreased by 40% from baseline at the end of the randomisation phase in the gammaCore group versus an increase of 1% in the standard of care only group, representing a 41% therapeutic benefit of gammaCore ($p<0.001$). *Response rate* – At the end of the randomised phase, a significantly higher number of people in the gammaCore group had attack frequency reductions from baseline (≥25% and ≥50% reduction, $p<0.001$; ≥75% reduction, $p<0.009$) compared with standard of care only. 3 people (8%) in the gammaCore group had a 100% attack frequency reduction versus 0% in the standard of care group.			as a cohort study in the assessment report.
Nesbitt et al (2015). Retrospective, non-comparative, cohort study. Location: UK (tertiary	19 people with cluster headache (11 with episodic cluster headache and 8 with chronic	gammaCore (used in addition to normal standard of care medication),	*Percentage change in other acute medication use* – high flow oxygen and parenteral triptans use	**Prevention** 15 patients reported overall improvement in their condition from baseline. The remaining 4 reported their condition remained the same.	6 people left the study, 2 due to failure to return signed summaries, 1 was lost to follow up, 1 due to equivocal diagnosis, 1 due	The study was funded by the company.	People included in this study could use their normally prescribed medications for cluster headache alongside gammaCore.

headache centre).	cluster headache).	no comparator. gammaCore protocol: Up to 3 consecutive doses for treatment of acute attack. For cluster headache prevention gammaCore was used to deliver 2/3 consecutive does, twice daily.	while using nVNS device *Percentage of attacks treated acutely Proportion of treatments able to terminate within 15 minutes of device use and time to do so* Follow-up period: January 2012 to December 2012	Results suggest a mean improvement of 48% (±9%). **Acute use** gammaCore aborted attacks in an average 11 mins (±1 min). 3 patients stopped using previous treatments, oxygen (n=2) or sumatriptan (n=1), in favour of nVNS. 10 patients reduced oxygen use by an estimated mean of 55% (±8%), 3 continued to use the same amount of oxygen and 1 patient reported an increase by 100%. 3 patients were able to stop using triptans but continued to use some oxygen. 9 patients reduced their use of triptans by a mean of 48% (±6%).	to having no treatable attacks and 1 due to poor compliance.		7 people included in the study were recorded as being treatment refractory to standard of care treatments for gammaCore. This study was conducted in an NHS tertiary headache centre. The small sample size, design (non-comparative) and the use if patient reported outcomes means that this study is possibly subject to bias. The EAC note that there may be a possible cohort overlap between this study and Marin et al. (2018).
Marin et al. (2018) Retrospective, non-comparative, cohort study. Location: 10 centres in UK	30 people with cluster headache (1 with episodic cluster headache and 29 with chronic cluster headache. All	gammaCore, no comparator. gammaCore protocol: initially based on instructions for use, as treatment	*gammaCore use Attack frequency, duration and severity* – rated on a 0–10 scale *Concomitant treatment use Safety*	*gammaCore use* 16 people (53%) used gammaCore as a preventative treatment only, 1 person (3%) used it as an acute treatment only and 13 people (43%) used it as	None.	The study was funded by the company. One of the authors is an employee	All people included in this study were treatment refractory to standard of care treatments for cluster headache. This study was conducted in 10 NHS centres.

	participants were treatment refractory to standard of care.	continued this was adjusted to suit individual needs.	Follow-up period: May 2012 to March 2016	both preventative and acute treatment. *Attack Frequency* Mean (range) attack frequency at baseline was 26.6 (3.8–77.0) attacks/week. This decreased to 9.5 (0–38.5) attacks/week with gammaCore (p<0.01) Attack Duration Mean duration of attacks decreased from 51.9 (5.0–140.0) mins at baseline to 29.4 (2.5–152.5) mins with gammaCore, p<0.01. *Attack Severity* Mean attack severity decreased from 7.8 (3.0–10.0) at baseline to 6.0 (1.0–10.0) with gammaCore, p<0.01 *Medication use* 3 people were able to manage their condition with preventative pharmacological treatment only and 4 were able to use gammaCore as a monotherapy.		of the company.	The small sample size, design (non-comparative) and the use if patient reported outcomes means that this study is possibly subject to bias. The EAC note that there may be a possible cohort overlap between this study and Nesbitt et al. (2015).
Trimboli et al. (2018)	12 people with chronic cluster headache. All	gammaCore, no comparator.	*Response rate – defined as ≥30%* reduction in	*Preventative use –* 1 person showed ≥30% reduction in weekly cluster	None.	The company provided	All people included in this study were treatment refractory

Prospective, non-comparative cohort study. Location: UK (tertiary headache centre).	participants were treatment refractory to standard of care.	gammaCore protocol: 2 consecutive doses (lasting 90 secs each), 3 times a day (prevention), up to 3 additional consecutive doses for acute treatment.	headache days after 3 months treatment *Change in headache severity* – including patients subjective impression of change *Treatment compliance* *Safety and tolerability*	headache frequency at month 3 compared with baseline. This person also reported a reduction in oxygen use. 2 people reported a slight improvement from baseline. 3 people reported no change. 6 people reported a worsening in weekly frequency. *Acute use* – No patients reported acute cluster headache relief using gammaCore. *Treatment Continuation* 1 person continued with gammaCore for 10 months but reported a worsening of their condition for 3 consecutive months and discontinued treatment.		the devices for a 3-month trial period and were responsible for training patients in the use of the device. Several of the authors have received grants from the company.	to standard of care treatments for cluster headache. This study was conducted in an NHS tertiary headache centre. The full study cohort was 42 patients, however, this included people with migraine and other headaches, the results are presented for the 12 people with cluster headache only. The small sample size, design (non-comparative) and the use if patient reported outcomes means that this study is possibly subject to bias.

4.2 Summary of economic evidence

No published relevant economic studies were identified by the company or by the EAC. The company and the EAC identified several publications that were not directly relevant to the decision problem but do provide context and validation for the de novo model. The EAC has summarised these studies in section 4.4 of the assessment report.

De novo analysis

The company created a de novo cost analysis using a Markov model (see figure 1, assessment report) with a 1-month cycle and 1-year time horizon. The model only considers people with chronic cluster headache and does not include people with episodic cluster headache.

The intervention in the model is gammaCore in addition to standard care for treatment of acute cluster headache attacks. Standard care medications comprised oxygen, zolmitriptan and sumatriptan. Preventative medication (e.g. verapamil) is not included in the model as this is assumed to be the same for both arms of the model. Sphenopalatine ganglion nerve stimulators and occipital nerve blocks are not included in the model as it is likely that gammaCore will be used before more invasive options are considered.

The model assumes that all gammaCore users will be using the device for 2 stimulations, 3 times a day which is in line with the clinical trials and instructions for use.

Model parameters

The model classifies patients as either responders or non-responders, based on data collected during Gaul et al. (2016). A responder is defined as someone who experiences at least a 50% reduction in frequency of attacks. The following table shows the proportion of patients in each state in the first and subsequent months.

	gammaCore in addition to standard of care	**Standard of care only**

	Responder (%)	Non-responder (%)	Responder (%)	Non-responder (%)
1st month	40	60	8	92
Subsequent months	27.6	72.4	0	100

Costs and resource use

The cost of gammaCore in the model is based on the current charging model where the technology is available for a 3-month (93 days) free trial period. People who benefit from using gammaCore in this trial period can then be supplied with an RFID card every 3 months. This RFID card is used to activate the gammaCore device so that it can deliver another 93 days of therapy. The device can then deliver a maximum of 30 stimulations in each 24-hour period. A conductive gel is also provided with each new RFID card, this is provided by the company free of charge and additional gel can be provided if requested. Training for patients and staff id provided by the company, free of charge.

The resource use for the comparator technologies is based on the distribution of rescue medication (sumatriptan, zolmitriptan and oxygen) recorded in the last 14 days of the PREVA trial (Gaul et al. 2016). Table 10 of the assessment report describes the proportions of patients receiving each treatment in each arm of the model.

The EAC note that no resource use is modelled for inpatient, outpatient or GP resources associated with attacks. The model also does not consider the cost of psychological support required to cope with results of chronic unresponsive cluster headaches, if gammaCore is effective it would be expected to improve these outcomes and reduce associated costs.

Results

The EAC did not make any changes to the cost model, and the results are presented in the following table.

Base case results for 1st year of use

	gammaCore in addition to standard of care (£)	Standard of care only (£)	Cost saving per patient (£) *(negative values indicate a cost saving)*
gammaCore	517.18	-	517.18
Sumatriptan	2,577.39	3,505.53	-928.13
Zolmitriptan	206.33	204.85	1.48
Oxygen	147.55	188.49	-40.95
Total	**3,448.45**	**3,898.86**	**-450.42**

The EAC adjusted the company's sensitivity analysis so that the one-way sensitivity analysis included all costs varying by 20% in either direction, and the costs for gammaCore in the first 3 months (free trial period) to vary between 0 and £625. This analysis showed that the costs for gammaCore and the use and cost of sumatriptan are the key drivers of the model. The cost savings depend on gammaCore's free trial period and reduced use of sumatriptan.

The EAC noted that the model for gammaCore is robust and would show a small cost saving even if no patients responded to treatment with gammaCore. However, the EAC also noted that the data underpinning the economic model is part of a single small data set and post hoc analysis that was only partially based in the UK.

5 Ongoing research

The company and the External Assessment Centre are not aware of any ongoing research on gammaCore.

The EAC has suggested that a clinical audit could be used to generate evidence on the benefits of gammaCore (section 8 of the assessment report).

6 Issues for consideration by the Committee

Clinical evidence

The current published evidence comprises 3 randomised trials and 4 cohort studies but not all of aspects of these studies are directly relevant to the

decision problem. However due to the small population size of cluster headache (and smaller proportion of people treatment refractory to standard care treatments), it may not have been possible to run randomised trials without the involvement of the company and a large, UK-based randomised trial is likely not possible.

All but one of the included clinical studies had some form of company involvement, the only study that did not (Trimboli et al. 2018) reported negative results

The subgroup analysis conducted in the ACT 1 and ACT 2 trials attempt to separate results by episodic and chronic cluster headache. The EAC suggest that this should be viewed with caution as the study was not powered for this analysis.

Cost evidence

Extensive post hoc analysis of patients into responder and non-responder groups was used to calculate resource use in the model. The EAC note that this has the possibility of introducing bias as not all patients were included and there are differences in population size between the PREVA study and the post hoc analysis.

Cost savings are driven by the free trial period for gammaCore and reductions in sumatriptan prescription.

7 Authors

Kimberley Carter, analyst

Bernice Dillon, technical adviser

NICE Medical Technologies Evaluation Programme

June 2019

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- O'Connell S et al. MT323 gammaCore for Cluster Headaches (May 2019)

B Submissions from the following sponsors:

- electroCore

C Related NICE guidance

D References

Please see EAC assessment report for full list of references.

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Dr Fayyaz Ahmed
Consultant neurologist, British Association for the Study of Headache

Dr Jane Anderson
Consultant neurologist, Buckingham Healthcare Trust

Dr Brendan Davies
Consultant neurologist and clinical lead, Midlands Regional Headache Clinic

Dr Alok Tyagi
Consultant neurologist, British Association for the Study of Headache

Dr Mark Weatherall
Consultant neurologist, Buckingham Healthcare Trust

Please see the clinical expert statements included in the pack for full details.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded:

- OUCH (Organisation for the Understanding of Cluster Headache)
- The Migraine Trust
- 82 responses from individual patients to NICE's online survey

Please see the patient expert statements included in the pack for full details.

Appendix D: decision problem from scope

	Final scope issued by NICE
Population	People over the age of 18 with cluster headache for whom standard care is ineffective or contraindicated.
Intervention	gammaCore
Comparator(s)	• Subcutaneous or nasal spray triptan therapy (acute) • Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute) • Verapamil (preventative) • Sphenopalatine ganglion nerve stimulators (acute and preventative treatment for chronic cluster headache) • Occipital nerve block (preventative)
Outcomes	The outcome measures to consider include: • Frequency, severity and duration of acute episodes of cluster headache • Time taken to relieve pain of acute episode (acute use) • Average response rate and proportion of patients at 50% and 75% response rate • Number of times device used for daily prevention • Number of times device used for acute treatment • Patient reported pain and disability scores • Patient health-related quality of life, including impact on occupation and employment • Patient satisfaction • Reduction of ECG and blood testing for monitoring of drug treatments • Use of outpatient and healthcare services, including psychiatric care • device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• Acute treatment of cluster headache • Prevention of cluster headache • Episodic cluster headache • Chronic cluster headache
Special considerations, including those	People with cluster headache are likely to be described as disabled because it is a chronic condition which is likely to last longer than 1 year. This technology has the potential to avoid invasive treatments

related to equality	(such as sphenopalatine ganglion nerve stimulation implants) or avoid the use of unlicensed medications with potentially serious side effects.	
Special considerations, specifically related to equality issues	Self-administration of treatment with gammaCore needs manual dexterity and the ability to follow instructions. gammaCore cannot be used by people with cochlear implants or pacemakers and has not been used in people who are pregnant, lactating or aged under 18 years.	
	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	Yes
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
	The committee will need to consider that gammaCore cannot be used by people included in the above statement.	

NICE National Institute for Health and Care Excellence

Adoption scoping report: MT323 gammaCore for cluster headache

Summary

Adoption levers

- May benefit patients when standard treatments are ineffective, not tolerated or contraindicated.
- Fewer side effects compared to standard options, such as triptan and verapamil
- Not invasive

Adoption barriers

- Cost
- Perceived poor quality of evidence to support its use

1. Introduction

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt gammaCore into routine NHS use.

2. Contributors

Adoption information was gathered from the manufacturer and 7 NHS staff in the following areas:

- 5 consultant neurologists who provide specialist headache services
- 1 consultant neurologist and neurophysiologist who provides a specialist headache service
- 1 neurology nurse specialist

All NHS contributors have experience of using gammaCore. This varied from 3 patients in the past year to 100 patients over the past 5 years.

3. Current pathway

All the contributors use gammaCore within regional specialist headache services that accept referrals directly from GPs or A&E departments. They reported that some

regional specialist headache services only accept referrals from consultant neurologists. Patients can be offered gammaCore at first visit if they have commenced standard treatment elsewhere. No additional appointments are usually required to introduce the technology.Contributors use gammaCore for both prevention and treatment of cluster headache acute attacks.

Users are advised on a preventative stimulation regime tailored to their pattern of cluster headache occurrence with additional use in the case of an acute attack. Contributors differed on whether they advised limiting the number of stimulations during an acute attack with one contributor reporting that they have a patient who sometimes uses 2 stimulations up to 15 times per day.

If gammaCore is not effective, patients may be referred to a neurosurgery service for procedures such as sphenopalatine ganglion (SPG) block, occipital nerve stimulation (ONS) and deep brain stimulation (DBS). The number of patients referred to a neurosurgery service varied among contributors.

4. Reported benefits

The benefits of adopting gammaCore, as reported to the adoption team by the healthcare professionals using the technology are:

- May help people for whom standard treatments are ineffective, not tolerated or contraindicated.
- Fewer side effects compared to standard options, such as triptan and verapamil
- Non-invasive treatment

5. Insights from the NHS

Patient selection

Most contributors would offer gammaCore to those people for whom standard treatments are ineffective, not tolerated or contraindicated. One contributor would prescribe gammaCore alongside standard treatment options in some people with a high frequency of attacks.

Clinician confidence

The predicted percentage of people with cluster headaches benefiting from gammaCore varied from 8% to 50%. All contributors agreed gammaCore was a useful treatment option but that it is not effective for everyone. One contributor stated that as cluster headache is both severe and disabling and that gammaCore provided another option for treatment that can alleviate the burden on the service and restore people's ability to function quickly.

Some contributors criticised the quality of research and study design available for gammaCore, particularly the alternative sham used in some studies.

Commissioning

None of the contributors have a budget for providing gammaCore and stated this was the main barrier to adoption.

The manufacturer offers a 3 month trial period. If the therapy is effective, contributors have applied for funding to the relevant clinical commissioning group (CCG) through an individual funding request (IFR) for where a treatment or service is not routinely offered by the NHS. A majority of patients have been refused IFR funding due to lack of exceptional clinical circumstances for gammaCore. Other contributors have funded gammaCore through clinical trials and some patients have self-funded.

Resource impact

One contributor suggested that there may be cost savings for appropriately selected users who benefit from gammaCore as this could prevent the need for referral to a

tertiary neurosurgery service and the associated costs met by the CCG including travel, hotels, consultations and interventions.

Another contributor suggested that there may be cost savings when compared with using verapamil which requires people to attend additional outpatient appointments every 2 weeks for electrocardiogram monitoring during long term use. gammaCore does not require this.

Training

Most contributors report that training for patients has been provided by the manufacturer through home visits, video conference or by phone.

Nurses in some services have had a 2 hour training session with the manufacturer and then trained people in clinic with the support of a short manufacturer produced video if required.

Governance

Some trusts have required gammaCore to be approved by an internal governance committee that approves the use of new technologies and it is reported that this can take between 1 and 3 months.

Patient experience

Some patients have attended clinic requesting gammaCore as a treatment option. Awareness has been raised from websites such as Ouch UK.

Contributors report that when gammaCore is effective, most people have preferred it over standard treatments due to fewer side effects and being non-invasive.

One contributor reported that some patients experience a higher frequency of attacks than the maximum dose allowed for standard treatment medication. For example, if someone has 6 attacks a day, sumatriptan 6mg by subcutaneous injection will cover 2 attacks, or zolmitriptan 5mg by intranasal administration will cover 3 attacks. Oxygen therapy may be difficult to use for the other attacks while the patient is at work, so gammaCore has been useful in these situations to help alleviate the pain.

Another contributor reported some patients reported drooping of the mouth while using gammaCore, which stopped when stimulation stopped.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: gammaCore™ for treating Cluster Headache

Sponsor: electroCore, Inc.

Date sections A and B submitted: 17-18 March 2019

Date section C submitted: 12 April 2019

August 2011 (Version 1.1)

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]'). Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked ‘Response’ or in the tables as appropriate. ‘Response’ text may be deleted.

List of tables and figures

List of Tables

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Glossary of terms

Term	Definition
AAN	American Academy of Neurology
ADE	adverse device effect
A&E	accident and emergency
AE	adverse event
ANCOVA	analysis of covariance
BASH	The British Association for the Study of Headaches
BMJ	*British Medical Journal*
CASP	Critical Appraisal Skills Programme
CCG	clinical commissioning group
cCH	chronic cluster headache
CH	cluster headache
CHF	congestive heart failure
CI	confidence interval
CRD	Centre for Reviews and Dissemination
CM	chronic migraine
CONSORT	Consolidated Standards of Reporting Trials
CVA	cerebral vascular attack
DARE	Database of Abstracts of Reviews of Effects
ECG	electrocardiogram
eCH	episodic cluster headache
ED	emergency department
EED	Economic Evaluation Database
EHF	European Headache Federation
EQ-5D-3L	3-level version of the EuroQol 5-dimension scale
eCH	episodic cluster headache
FDA	Food and Drug Administration
FOI	freedom of information
gCore	gammaCore
GDPR	General Data Protection Regulation (EU) 2016/679
GEE	generalised estimating equation
GMC	General Medical Council
GP	general practitioner
HIPAA	Health Insurance Portability and Accountability Act
HIT-6	6-item Headache Impact Test
HRG	Healthcare Resource Groups
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICHD	International Classification of Headache Disorders
ICTRP	International Clinical Trials Registry Platform

Term	Definition
IFR	individual funding request
IHS	International Headache Society
ISO	International Organization for Standardisation
ITT	intent-to-treat
LOCF	last observation carried forward
MeSH	medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
mITT	modified intent-to-treat
N/A	not applicable
NCT	National Clinical Trial
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIH	National Institutes of Health
NR	not reported
nVNS	non-invasive vagus nerve stimulation
ONS	occipital nerve stimulation
OPCS	Office of the Population, Censuses and Surveys Classification of Surgical Operations and Procedures
OR	odds ratio
OWSA	one-way sensitivity analysis
PAC	premature atrial contraction
PbR	payment by results
PP	per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
PVC	premature ventricular contraction
QALY	quality-adjusted life-year
QoL	quality of life
QTc	corrected QT
RCT	randomised controlled trial
SA	sinus arrhythmia
SADE	serious adverse device effect
SAE	serious adverse event
s.c.	subcutaneous
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SoC	standard of care
SPG	sphenopalatine ganglion

Term	Definition
SUNA	short-lasting unilateral neuralgiform headache attacks with autonomic symptoms
TAC	trigeminal autonomic cephalalgia
TIA	transient ischemic attack
Tx	treatment
VAT	value-added tax
VNS	vagus nerve stimulation
WHO	World Health Organisation

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1: Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People over the age of 18 with cluster headache for whom standard care is ineffective or contraindicated		
Intervention	gammaCore		
Comparator(s)	• Subcutaneous or nasal spray triptan therapy (acute) • Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute) • Verapamil (preventive) • Sphenopalatine ganglion nerve stimulators (acute and preventive treatment for chronic cluster headache) • Occipital nerve block (preventive)		
Outcomes	The outcome measures to consider include the following: • Frequency, severity, and duration of acute episodes of cluster headache • Time taken to relieve pain of acute episode (acute use) • Average response rate and proportion of patients at 50% and 75% response rates • Number of times device used for daily prevention • Number of times device used for acute treatment • Patient reported pain and disability scores • Patient health-related quality of life, including impact on occupation and employment • Patient satisfaction • Reduction of ECG and blood testing for monitoring of drug treatments		

	Scope issued by NICE	Variation from scope	Rationale for variation
	• Use of outpatient and healthcare services, including psychiatric care • Device-related adverse events		
Cost analysis	Costs will be considered from NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	• Acute treatment of cluster headache • Prevention of cluster headache • Episodic cluster headache • Chronic cluster headache		
Special considerations, including issues related to equality	People with cluster headache are likely to be described as disabled because it is a chronic condition that is likely to last longer than 1 year. This technology has the potential to avoid invasive treatments (such as sphenopalatine ganglion nerve stimulation implants) or the use of unlicensed medications with potentially serious side effects. Self-administration of treatment with gammaCore requires manual dexterity and the ability to follow instructions. gammaCore cannot be used by people with cochlear implants or pacemakers and has not been used in people who are pregnant, lactating, or under 18 years.		

2 Description of technology under assessment

2.1 Brand name, approved name and details of any different versions of the same device

gammaCore™, gammaCore Sapphire™.

2.2 Principal mechanism of action of the technology

Non-invasive vagus nerve stimulation (nVNS).

3 Clinical context

3.1 Brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE

Cluster headache (CH) is a primary headache disorder included in a group of conditions called trigeminal autonomic cephalalgias (TACs). CH attacks are characterised by excruciating unilateral head pain that occurs in series that can last for weeks, months, or years (Wei et al. 2018). Attack frequency varies from one event every other day to more than six attacks per day, with bouts of pain typically endured for 15 minutes to three hours (Headache Classification Committee of the International Headache Society. 2018, Wei et al. 2018). CH is the most severe of primary headache disorders, recently recognised by the NHS as one of the most painful conditions known to man (Mandal. 2018). It has been called the “suicide headache” because some people have taken their lives either during an attack or in anticipation of an attack, and suicidal ideations have been reported in 55% of surveyed cluster headache patients (Rozen and Fishman. 2012).

CH affects 0.1% of the population (66,000 people in the UK), with experts in the field suggesting that approximately 5% of these people do not have enough symptom control with standard care (NICE. 2018a, Wei et al. 2018). CH predominantly affects men aged 20 years and older, and persons at greater risk of CH include heavy smokers and those with a family history of the condition (Wei et al. 2018).

CH may be episodic (eCH) or chronic (cCH) and can often change between the two types. eCH is defined by attack periods that can last from 7 days to 1 year and are separated by a month-long pain-free period. Episodic headaches often recur predictably during certain times of the year. cCH attack periods are recurrent for more than 1 year, and headaches can be separated by headache-free periods of less than 3 months or may not be separated at all (Wei et al. 2018).

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

- *gammaCore for cluster headache*. Medtech innovation briefing published by NICE in October 2018 (NICE. 2018a)
- *Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine*. Interventional procedures guidance published by NICE in March 2016 (NICE. 2016)
- *Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache*. Interventional procedures guidance published by NICE in June 2015 (NICE. 2015)
- *Deep brain stimulation for intractable trigeminal autonomic cephalalgias.* Interventional procedures guidance published by NICE in March 2011 (NICE. 2011)
- The Northern (NHS) Treatment Advisory Group recommends the use of non-invasive transcutaneous vagus nerve stimulation (gammaCore) for the treatment of cluster headache (NHS England. 2018)

3.3 Clinical pathway of care that includes the proposed use of the technology

NICE's clinical guideline on headache states that oxygen or triptans should be used for acute treatment of cluster headache (NICE. 2018b). These treatments can be effective at relieving pain within 15-30 minutes. The guideline states that paracetamol, NSAIDs, opioids, ergots, or oral triptans should not be offered for the acute treatment of cluster headache because they are not effective. The guideline recommends that verapamil be prescribed for long-term prophylaxis and that ECG monitoring should be offered to patients receiving verapamil. Oral steroids (e.g. prednisolone) may also be prescribed as monotherapy or alongside verapamil but can be used

only for a short time because of side effects. Anticonvulsants may also be prescribed. The use of verapamil and anticonvulsants for cluster headache is outside their marketing authorisation.

When other treatments fail, invasive treatments such as surgically implanted vagus nerve stimulators, deep brain stimulators (which require neurosurgery), occipital nerve stimulators, and sphenopalatine ganglion stimulators (NICE. 2015) may be considered.

NICE interventional procedures guidance on transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine recommends that the procedure be used only with special arrangements for clinical governance, consent and audit, or research (NICE. 2016).

Expert advice indicates that many people with cluster headache do not get enough pain relief with current treatment options, which are often limited by side effects and contraindications. gammaCore is intended for use by people with cluster headache for whom standard treatment has been unsuccessful or in people who cannot use other prescribed treatments. If used, it is most likely to be introduced before more invasive procedures or treatment with lithium are considered. gammaCore is most likely to be prescribed by neurologists in tertiary centres who specialise in headache management. People using gammaCore will need brief training, which is provided by the company at no extra cost. Once trained, people with cluster headache can use gammaCore in any setting.

3.4 Any issues relating to current clinical practice, including any uncertainty about best practice

There is currently no prospect of a curative treatment for cluster headache. The attainable goal of treatment is total attack cessation or suppression of the headache until the next episode. A more conservative and realistic goal is to shorten the cluster period in eCH and to reduce the severity/frequency in both eCH and cCH. This is currently attempted using pharmacological medicine,

both prophylactically and as acute treatments (British Association for the Study of Headache. 2010).

Verapamil and lithium are often prescribed as prophylactic medicines, but neither is authorised for this use. Furthermore, verapamil requires gradual titration in order to minimise the risk of third-degree atrioventricular block, and close ECG monitoring should be offered during this titration. The use of these prophylactic medicines is not supported by a formal clinical evidence base, and their use is completely empirical.

The BASH has published guidelines for the management of CH (British Association for the Study of Headache. 2010). Therapies are prescribed to attempt to prevent or decrease CH attacks (prophylaxis) and to manage pain at the time of a CH attack (acute/abortive treatment); the latter is rarely sufficient to achieve adequate control alone. Not all experts use therapies in the same order, and in some cases, occipital nerve blockade is also used for prevention of CH.

3.5 The new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England

If gammaCore is adopted by the NHS in England, the current pathway of care for CH patients would not change. The availability of gammaCore would provide clinicians and patients with an authorised, clinically proven, non-pharmacological treatment option that could be easily used by patients as both prophylactic and acute therapies. Its intended place in therapy would most likely be where standard care treatments for cluster headache are ineffective, not tolerated, or contraindicated.

3.6 Any changes to the way current services are organised or delivered as a result of introducing the technology

People prescribed gammaCore require brief training to ensure its correct use. Training can be provided by the NHS-based headache team (neurologist or headache nurse) or by the company via video call or through resources

available at all times on the internet. No changes to the way current services are organised and delivered should be required.

3.7 Any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice

No additional tests, investigations, or monitoring are required.

When authorising the use of gammaCore, clinicians must gain consent from patients, which allows sharing of the patients' basic personal information (name, address, and contact details). This is done using a General Data Protection Regulation (GDPR)-compliant form that is e-mailed to the company. This step allows the company to send the gammaCore device directly to the patient and provide additional training when required. This administrative step is a minor one and may add a couple of minutes to the consultation time, at most.

3.8 Any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised

None.

3.9 Any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology

gammaCore can be used as both prophylactic and acute treatments. When gammaCore is used as a prophylactic therapy, verapamil and the associated ECG monitoring during verapamil titration may no longer be needed. This ECG monitoring typically takes place in primary care facilities so will reduce this GP/community nursing team appointment pressure. Hospital outpatient appointments, accident and emergency (A&E) attendance, and telephone

consultation may also be reduced as a consequence of improved prophylactic control of CH. Prophylactic use of gammaCore has been shown to significantly decrease the use of both triptans and oxygen during acute attacks, allowing economic and quality of life benefits to be realised for payers and patients, respectively (Gaul et al. 2016). The limitations associated with home-based oxygen cylinders from environmental, safety, and delivery logistics perspectives may also be removed.

Prior to the availability of gammaCore, many patients with treatment-refractory CH may have been referred to a tertiary centre, where a complex invasive surgical procedure may have been undertaken to achieve treatment success. gammaCore can eliminate a significant number of these unnecessary, expensive interventions.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

If gammaCore is adopted, use of the tests, investigations, interventions, facilities, or technologies described in section 3.9 would gradually be reduced over time. A disinvestment strategy would not be needed because these activities would decrease as a direct result of clinicians and patients choosing gammaCore.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- Instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- Quality systems (ISO 13485) certificate (if required).

The documents have been provided with this submission.

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

- gammaCore and gammaCore Sapphire are indicated for the acute and/or prophylactic treatment of primary headaches (migraine, cluster headache, and hemicrania continua) and medication overuse headache in adults.
- Authorisation was received on 30 August 2011.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

- In the US, the Food and Drug Administration (FDA) provided clearance for adjunctive use of gammaCore for the preventive treatment of cluster headache in November 2018, making gammaCore the first and only therapy available for the prevention of cluster headache (electroCore. 2018). gammaCore was FDA cleared for the relief of pain associated with migraine in 2018 and eCH in 2017 (electroCore. 2018).

- gammaCore currently holds five CE marks for use in the EU in the following indications: primary headache, bronchoconstriction, epilepsy, gastric motility disorders, and depression and anxiety.

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Not applicable.

4.5 If the technology has been launched in the UK provide information on the use in England.

gammaCore is most regularly utilised in the following NHS Hospital Trusts; others may have recently started authorising gammaCore but are not included in the list:

- The Walton Centre NHS Foundation Trust, Liverpool
- University Hospitals of North Midlands NHS Trust, Royal Stoke University Hospital
- The Mid Yorkshire Hospitals NHS Trust, Pinderfields Hospital, Wakefield
- Queen Elizabeth University Hospital, Glasgow
- Hull & East Yorkshire Hospitals NHS Trust
- Royal United Hospitals Bath NHS Foundation Trust
- Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's, Cambridge
- Kings College Hospital NHS Foundation Trust, London
- St George's Hospital, London
- Guy's and St Thomas' NHS Foundation Trust, London
- The National Hospital for Neurology and Neurosurgery, London
- Oxford University NHS Foundation Trust, John Radcliffe Hospital, Oxford
- Northampton General Hospital NHS Trust, Northampton

- Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth
- Gloucestershire Hospital NHS Foundation Trust, Gloucester Royal Hospital, Gloucester
- North Bristol NHS Trust, Southmead Hospital, Bristol
- Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Newcastle
- City Hospitals Sunderland NHS Foundation Trust, Sunderland Royal Hospital, Sunderland
- University Hospitals Birmingham NHS Foundation Trust, NHS Queen Elizabeth Hospital, Birmingham
- Imperial College Healthcare NHS Trust, Charing Cross Hospital, London

gammaCore is available for patients to privately purchase following authorisation by an appropriate named General Medical Council (GMC)-registered healthcare professional.

5 Ongoing studies

5.1 Details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months

Dr. Manjit Matharu of The National Hospital for Neurology and Neurosurgery in London is in the process of writing and submitting a study examining the effectiveness of non-invasive vagus nerve stimulation (gammaCore) in patients with chronic cluster headache.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

None.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Any equality issues relating to the patient population and condition for which the technology is being used

People with cluster headache are often described as disabled because it is a chronic condition that is likely to last longer than 1 year. The gammaCore technology avoids invasive treatments or use of unlicensed medications with potentially serious side effects. Self-administration of treatment with gammaCore requires manual dexterity and the ability to follow instructions. gammaCore cannot be used by people with cochlear implants or pacemakers and has not been used in people who are pregnant, lactating, or younger than 18 years.

6.1.2 Any equality issues relating to the assessment of the technology that may require special attention

None.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

Not applicable.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Strategies used to retrieve relevant clinical data from the published literature

The Medline, Embase, Medline (R) In-Process, and Cochrane Library databases were searched for all clinical studies of non-invasive vagus nerve stimulation (nVNS) in the treatment and prevention of cluster headache that were published between 1 January 2005 and 21 February 2019. Full details on the search strategy are provided in section 10, appendix 1.

Unpublished studies

7.1.2 Strategies used to retrieve relevant clinical data from unpublished sources

On 28 February 2019, the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP) databases were searched for all clinical studies of nVNS in the treatment and prevention of cluster headache. In the ClinicalTrials.gov search, “cluster headache” was specified for the condition or disease and “vagus nerve stimulation” OR “gammaCore” was specified for the intervention/treatment; no other search limits were defined. In the WHO-ICTRP, search terms were “cluster headache” AND “vagus nerve stimulation” OR “gammaCore,” and no other search limits were defined. Conference abstracts and presentations that were excluded from the published study search due to the absence of corresponding published articles were added to the unpublished study search results and are included with this submission.

Search results from each source were cross-referenced, and duplicates were removed to create a master list of unique records for screening. For studies represented by more than one record, only the record associated with the most recent date was selected for inclusion. Search results that clearly did not represent studies of nVNS use in cluster headache on the basis of the study title (e.g. migraine, healthy subjects) were excluded. The NCT numbers of the remaining records were then cross-referenced with those indicated in the final full-text articles from the published study search, and duplicate studies were removed from the unpublished study search results.

The eligibility of full-text records and/or abstracts was then assessed for the remaining search results. Records included were required to represent the evaluation of nVNS for the treatment or prevention of cluster headache. Records representing only post hoc analyses of a study were excluded and discussed only in section 7.4.2 (i.e. data from a single study drawn from more than one source). For remaining search results, any corresponding manuscript drafts in progress were obtained from company files of the sponsor, and the structured abstract was included with this submission.

Sources determined to be eligible for qualitative synthesis were reviewed, and each item detailed in this template was extracted and entered directly into the document. Data abstraction was verified by a second reviewer for accuracy and completeness.

7.2 Study selection

Published studies

7.2.1 Inclusion and exclusion criteria used to select studies from the published literature (Table B1)

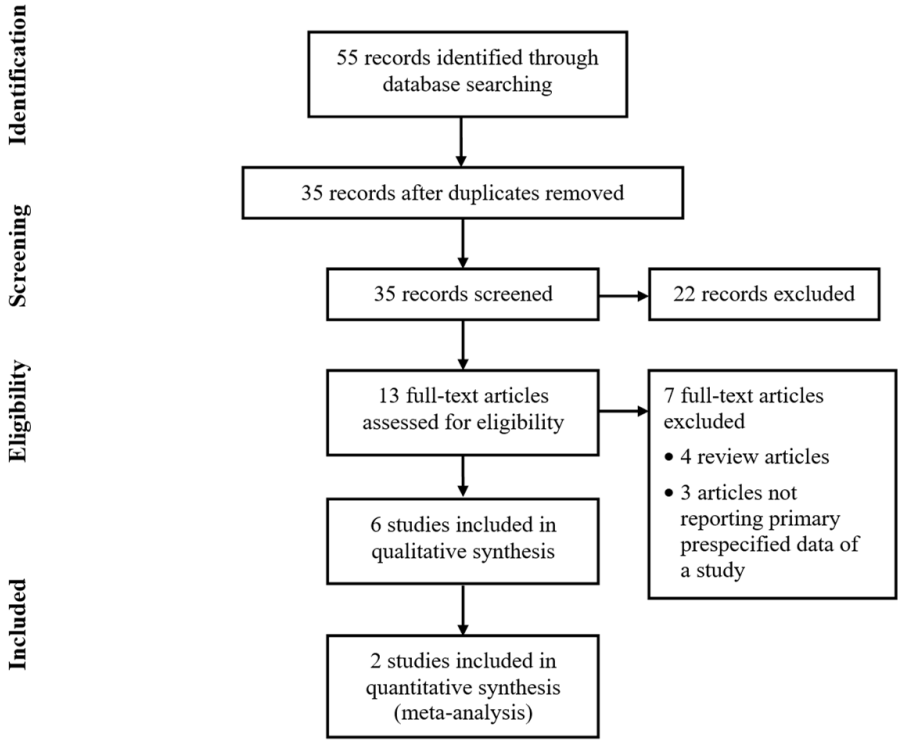
Table B1: Selection criteria used for published studies

Inclusion criteria	
Population	Cluster headache
Interventions	nVNS
Outcomes	All outcomes
Study design	Clinical trials
Language restrictions	English
Search dates	1 January 2005 through 21 February 2019
Exclusion criteria	
Population	Non−cluster headache disease states, healthy subjects
Interventions	Treatments other than nVNS
Outcomes	No exclusions
Study design	Post hoc analyses, non-primary study publications, mechanistic studies, reviews
Language restrictions	Non-English
Search dates	Prior to 1 January 2005

7.2.2 Numbers of published studies included and excluded at each stage

The numbers of published studies included and excluded at each stage are shown in Figure B1.

Figure B1: PRISMA diagram for published studies of nVNS for cluster headache



Unpublished studies

7.2.3 Inclusion and exclusion criteria used to select studies from the unpublished literature (Table B2)

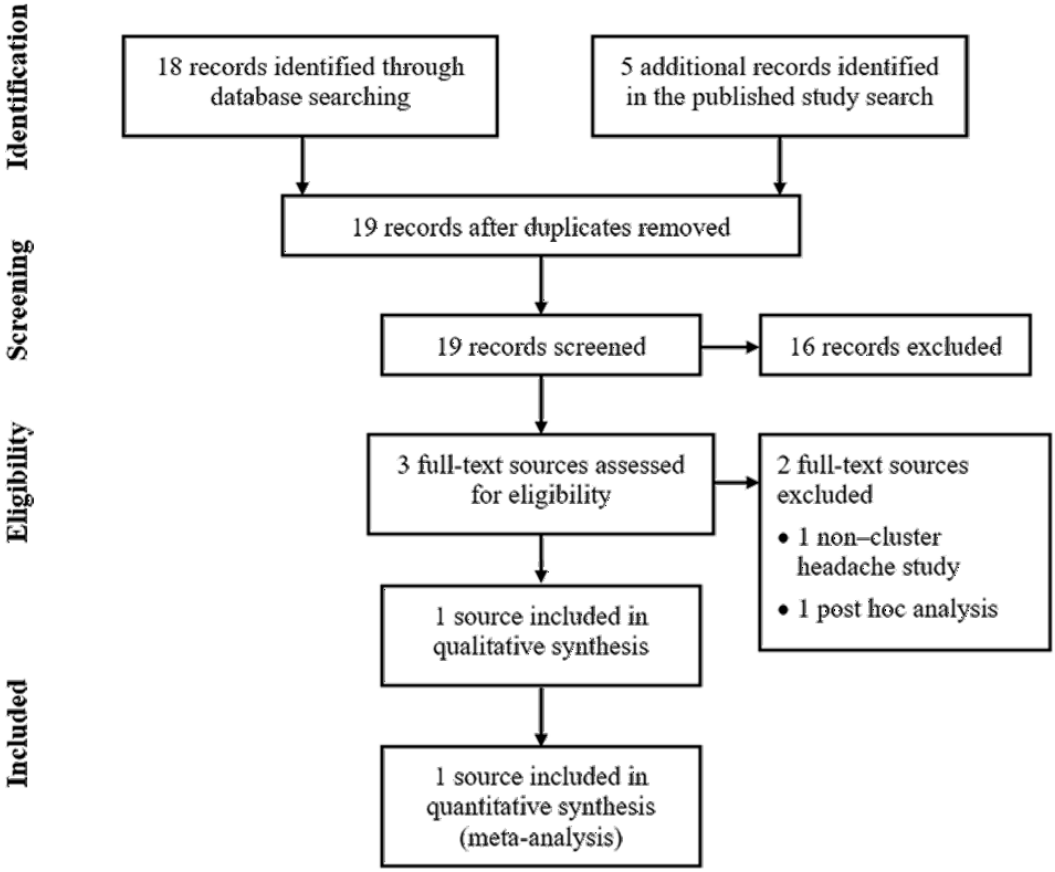
Table B2: Selection criteria used for unpublished studies

Inclusion criteria	
Population	Cluster headache
Interventions	nVNS
Outcomes	All outcomes
Study design	Clinical trials, evidence synthesis
Language restrictions	No restrictions
Search dates	All dates
Exclusion criteria	
Population	Non−cluster headache disease states, healthy subjects
Interventions	Treatments other than nVNS
Outcomes	No exclusions
Study design	Post hoc analyses
Language restrictions	No exclusions
Search dates	No exclusions

7.2.4 Numbers of unpublished studies included and excluded at each stage

The numbers of unpublished studies included and excluded at each stage are shown in Figure B2.

Figure B2: PRISMA diagram for unpublished studies of nVNS for cluster headache



7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Details of all published and unpublished studies identified using the selection criteria described in Tables B1 and B2

All published and unpublished studies selected in the systematic searches are presented in Table B3 and Table B4, respectively (Silberstein et al. 2016b, Goadsby et al. 2018, de Coo et al. 2017, Gaul et al. 2016, Marin et al. 2018, Nesbitt et al. 2015, Trimboli et al. 2018). The PREVA and Marin et al (2018) studies compared nVNS directly with appropriate comparators referred to in the decision problem (i.e. standard of care). Copies of all published studies and a structured abstract for the future publication of the one unpublished search result (along with the most recent corresponding conference abstract and poster presentation) are included with this submission.

Table B3: List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Silberstein SD, Mechtler LL, Kudrow DB, et al. *Headache*. 2016;56(8):1317-1332.	ACT1	Episodic and chronic cluster headache (US)	nVNS (acute)	Sham
Goadsby PJ, de Coo IF, Silver N, et al. *Cephalalgia*. 2018;38(5):959-969.	ACT2	Episodic and chronic cluster headache (EU)	nVNS (acute)	Sham
Gaul C, Diener CH, Silver N, et al. *Cephalalgia*. 2016; 36(6):534-546.	PREVA	Chronic cluster headache (EU)	SoC+nVNS (preventive)	SoC alone
Marin J, Giffin N, Consiglio E, et al. *J Headache Pain*. 2018;19(1):114.	Marin et al (2018)	Episodic and chronic cluster headache (UK)	SoC+nVNS (real-world, preventive)	SoC alone

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Nesbitt AD, Marin JC, Tompkins E, Ruttledge MH, Goadsby PJ. *Neurology*. 2015;84(12):1249-1253.	Nesbitt et al (2015)	Episodic and chronic cluster headache (UK)	nVNS (acute and preventive)	N/A
Trimboli M, Al-Kaisy A, Andreou AP, Murphy M, Lambru G. *Cephalalgia*. 2018;38(7):1276-1285.	Trimboli et al (2018)	Chronic cluster headache, chronic migraine, hemicrania continua, SUNA (UK)	nVNS (real-world, acute and preventive)	N/A

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care; SUNA, short-lasting unilateral neuralgiform headache attacks with autonomic symptoms.

Table B4: List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
de Coo IF, Marin JCA, Silberstein SD, et al. 30 January 2019.	de Coo et al (2019)	Episodic and chronic cluster headache (pooled analysis of ACT1 and ACT2)	nVNS (acute)	Sham

Abbreviation: nVNS, non-invasive vagus nerve stimulation.

7.3.2 Rationale behind excluding any of the published studies listed in tables B3 and B4

No studies listed in Tables B3 or B4 were excluded.

7.4 Summary of methodology of relevant studies

7.4.1 Study design and methodology for published and unpublished studies

Table B5: Summary of methodology for the ACT1 study

Study name	**ACT1**
Objectives	To evaluate nVNS as an acute CH treatment
Location	20 US centres, including university-based/ academic medical centres and headache/pain/neurological clinics and institutes
Design	Randomised, double-blind, sham-controlled prospective study
Duration of study	4 months (1-month double-blind phase; 3-month open-label phase)
Sample size	120 subjects (60 per treatment arm) provides 82% power (primary endpoint), with a significance level of $P \leq 0.05$ for a 2-sided test
Inclusion criteria	Adults with eCH or cCH according to ICHD, 2nd edition criteria; 18 to 75 years of age
Exclusion criteria	Key exclusion criteria were a history of aneurysm, intracranial haemorrhage, brain tumours, significant head trauma, prolonged QT interval, arrhythmia, ventricular tachycardia/fibrillation, syncope, or seizure; structural intracranial/cervical vascular lesions; another significant pain disorder; cardiovascular disease; uncontrolled hypertension; abnormal baseline electrocardiogram; botulinum toxin injections in the past 3 months; nerve blocks in the past 1 month; previous CH surgery, bilateral/right cervical vagotomy, carotid end arterectomy, or right vascular neck surgery; electrical device implantation; and current use of prophylactic medications for indications other than CH.
Method of randomisation	Using independent statistician–generated randomisation schedules, subjects were randomly assigned (1:1) to receive nVNS or sham treatment (variable block design, stratified by site).
Method of blinding	Investigators, subjects, and study coordinators were blinded to treatment assignments. Devices labelled with a 3-digit randomisation number were not outwardly identified as active or sham and were allocated to the sites by a third-party distributor according to the randomisation scheme. Trained study site personnel (investigator or study coordinator) distributed devices to subjects in chronological order according to the randomisation number.
Intervention(s) (n=) and comparator(s) (n=)	See Figure B3
Baseline differences	No differences were observed in baseline characteristics
Duration of follow-up, lost to follow-up information	1 month (double-blind phase); 3 months (open-label phase); 8 patients were lost to follow-up (Figure B3); no follow-up after end of study (i.e. open-label phase)
Statistical tests	Descriptive statistics were used for continuous variables. Categorical variables were summarized by frequency distribution and proportion; Clopper-Pearson (exact) 95% CIs were calculated for response rates. Group differences for the primary endpoint and other categorical variable comparisons were performed using the Fisher exact test (if expected frequency ≤5 for ≥1 cell) or the chi-square test. Linear mixed-effect regression models were used to compare mean treatment group intensities to account for repeated measures per subject. Attack duration comparisons were performed using the *t* test. Comparisons of within-subject response rates between the double-blind and open-label phases were performed using the McNemar test for paired proportions. Missing data were imputed as failures for response variables and using the last observation carried forward for attack intensity. Statistical significance was set at $P<0.05$. *P*-values are provided for the efficacy analyses of the total population as well as the eCH and cCH cohorts without adjustment for multiple comparisons.

Study name	**ACT1**
Primary outcomes (including scoring methods and timing of assessments)	Efficacy: Response rate is defined as the proportion of all subjects who achieved a pain intensity score of 0 or 1 on a 5-point scale (0, *no pain*; 4, *very severe pain*) at 15 minutes after treatment for the first CH attack in the double-blind phase. Differences in nVNS and sham response rates were assessed for the total population as well as for the eCH and cCH cohorts. Safety: Occurrence of SADEs
Secondary outcomes (including scoring methods and timing of assessments)	Efficacy (double-blind period): included sustained treatment response rate (i.e. proportion of subjects with a pain intensity score of 0 or 1 without rescue medication use at 15 through 60 minutes after treatment initiation for the first CH attack) and average of all subjects' mean pain intensities at 15 minutes after treatment initiation for all attacks (up to 5 attacks per subject). Differences in nVNS and sham outcomes were assessed for the total population as well as for the eCH and cCH cohorts. Safety: All AE occurrences

Abbreviations: AE, adverse event; cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; ICHD, International Classification of Headache Disorders; nVNS, non-invasive vagus nerve stimulation; SADE, serious adverse device effect.

Table B6: Summary of methodology for the ACT2 study

Study name	**ACT2**
Objectives	To confirm and extend the results from ACT1 (above) by examining additional clinical and patient-related endpoints in a European setting of nVNS as an acute CH treatment
Location	4 European countries at 9 tertiary care sites, including academic medical centres and headache/pain/neurology clinics
Design	Randomised, double-blind, sham-controlled prospective study
Duration of study	1-week run-in period; 2-week, randomised, double-blind period during which subjects were treated with nVNS or a sham device; and 2-week open-label period during which all subjects received nVNS therapy
Sample size	Assuming a response probability of 0.3 for the sham group and 0.6 for the nVNS group, a sample size of 54 per group, including a 10% margin for dropout, was determined to provide 80% power with respect to the primary endpoint.
Inclusion criteria	Adults with eCH or cCH according to ICHD, 2nd edition criteria; ≥18 years of age
Exclusion criteria	Individuals with eCH who were not in a bout at the time of screening and those who were pregnant, nursing, or thinking of becoming pregnant during the study or had an abnormal baseline electrocardiogram were excluded. Other exclusion criteria were the need to begin treatment with oral or injectable steroids for eventual concomitant medical conditions; a lesion, dysaesthesia, previous surgery, or abnormal anatomy at the treatment site; a history of cranial aneurysm, intracranial haemorrhage, brain tumour, significant head trauma, carotid endarterectomy, vascular neck surgery, or cervical vagotomy; diagnosed or suspected secondary headache or any other significant pain condition that might have confounded study assessments; use of any medication that might have interfered with the study; known or suspected atherosclerotic cardiovascular disease, severe carotid artery disease, congestive heart failure, known severe coronary artery disease, or recent (5 years) myocardial infarction; a recent (12 months) or repeated history of syncope or seizures; uncontrolled high blood pressure; an implanted electrical and/or neurostimulator device, metal cervical spine hardware, or metallic apparatus near the stimulation site; and a known or suspected history of substance abuse, addiction, or headache medication overuse or a psychiatric/cognitive condition that may have interfered with the study.
Method of randomisation	A standard design with a block size of 4 was used to randomly assign subjects to treatment with either nVNS or the sham device (1:1 ratio) in addition to their standard-of-care regimen during the double-blind period.
Method of blinding	Each site received sealed randomisation envelopes imprinted with subject numbers. Subjects were enrolled in consecutive order at each site. Unblinded trainers provided subjects with the appropriate device, as indicated by their randomisation envelope, and training on its use.

Study name	**ACT2**
Intervention(s) (n=) and comparator(s) (n=)	See Figure B4
Baseline differences	Baseline characteristics were generally similar between treatment groups.
Duration of follow-up, lost to follow-up information	1 week (run-in period); 2 weeks (double-blind period); 2 weeks (open-label period); 4 patients were lost to follow-up (Figure B4); no follow-up after end of study (i.e. open-label phase)
Statistical tests	For the double-blind period, the primary efficacy endpoint was evaluated using generalised estimating equations with treatment group and study site as independent factors, except in the eCH cohort analysis, which was not adjusted for study site. A type 3 test of fixed effects was conducted to evaluate the interaction between treatment group and CH subtype. Mean proportions of treated attacks per subject that achieved responder status and that achieved pain-free status within 30 minutes were compared between treatment groups using the Wilcoxon rank sum test with stratification by study site. Mean changes in pain intensity between attack onset and subsequent time points were evaluated via 2-sided *t* tests. Proportions of subjects who achieved pain-free status for ≥50% of treated attacks and who achieved responder status for ≥50% of treated attacks at 15 minutes were assessed using the chi-square or Fisher exact test, as appropriate.
Primary outcomes (including scoring methods and timing of assessments)	Efficacy: The primary endpoint (double-blind period) was the proportion of all treated attacks that achieved pain-free status (i.e. pain score of 0) within 15 minutes after treatment initiation. Safety: AE occurrences
Secondary outcomes (including scoring methods and timing of assessments)	Secondary efficacy endpoints (double-blind period) included the mean proportion of treated attacks per subject that achieved responder status (i.e. pain score of 0 or 1) within 30 minutes, mean proportion of treated attacks per subject that achieved pain-free status within 30 minutes, and mean change in pain intensity from attack onset to 15 and 30 minutes after treatment initiation.

Abbreviations: AE, adverse event; cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; ICHD, International Classification of Headache Disorders; nVNS, non-invasive vagus nerve stimulation.

Table B7: Summary of methodology for the de Coo et al (2019) study

Study name	**de Coo et al (2019)**
Objectives	To conduct a pooled analysis of efficacy, safety, and tolerability data of nVNS as an acute CH treatment from ACT1 and ACT2 studies (above)
Location	20 US centres and 9 tertiary care sites (in 4 European countries)
Design	Pooled analysis of 2 randomised, double-blind, sham-controlled prospective studies
Duration of study	ACT1: 4 months (1-month randomised phase; 3-month open-label phase); ACT2: 5 weeks (1-week run-in period; 2-week randomised double-blind period; 2-week open-label period)
Sample size	ACT1: 120 subjects (60 per treatment arm) provided 82% power (primary endpoint), with a significance level of $P \leq 0.05$ for a 2-sided test. ACT2: A sample size of 54 per group, including a 10% margin for dropout, was determined to provide 80% power with respect to the primary endpoint (response probability of 0.3 for the sham group and 0.6 for the nVNS group).
Inclusion criteria	See Table B5 and Table B6
Exclusion criteria	See Table B5 and Table B6
Method of randomisation	Randomly assigned (1:1) to receive nVNS or sham treatment (ACT1, variable block design; ACT2, block size of 4)

Study name	**de Coo et al (2019)**
Method of blinding	See Table B5 and Table B6
Intervention(s) (n=) and comparator(s) (n=)	225 participants in the pooled analysis, 133 from ACT1 and 92 from ACT2, who were randomly assigned to nVNS (n=108) or sham (n=117)
Baseline differences	No differences were observed in baseline characteristics.
Duration of follow-up, lost to follow-up information	ACT1: 1 month (double-blind phase); 3 months (open-label phase); 8 patients were lost to follow-up (Figure B3); no follow-up after end of study (i.e. open-label phase) ACT2: 1 week (run-in period); 2 weeks (double-blind period); 2 weeks (open-label period); 4 patients were lost to follow-up (Figure B4); no follow-up after end of study (i.e. open-label phase)
Statistical tests	Logistic regression models were used to estimate odds ratios and associated 95% CIs for (i) the proportion of participants with pain relief for first treated attack at 15 minutes after treatment initiation (the ACT1 primary endpoint) and (ii) the proportion of participants who had pain relief in ≥50% of all treated attacks at 15 minutes after treatment initiation. Analyses resulting in pooled estimates included site as a covariate in the logistic regression models. Generalised linear mixed-effects regression models were used to estimate the proportion of all treated attacks that had pain relief at 15 minutes after treatment initiation for that attack (the ACT2 primary endpoint), allowing for both participant-specific and population-averaged inferences in non-normally distributed data. The structure of the covariance matrix was specified as compound symmetry. For both models, a fixed effects meta-analysis was used to estimate the pooled effects of nVNS treatment because the ACT1 and ACT2 studies were homogeneous for participant populations and results; study was included as a fixed effect for both pooled analyses. *P*-values for comparisons between the nVNS and sham groups were determined from resulting *F* tests. First-order interactions between treatment group and CH subtype were examined to determine whether the magnitude of treatment effect varied significantly by CH subtype. 2-sided *P*-values <0.05 were considered statistically significant.
Primary outcomes (including scoring methods and timing of assessments)	Primary outcomes for the pooled analysis were those of the ACT1 and ACT2 studies. ACT1: The proportion of participants whose first treated attack had improved (on a 5-point pain intensity scale) from pain intensity of moderate (2), severe (3), or very severe (4) to mild (1) or nil (0) at 15 minutes after treatment initiation ACT2: The proportion of all treated attacks that had improved from pain intensity of 2-4 to 0 at 15 minutes after treatment initiation for that attack
Secondary outcomes (including scoring methods and timing of assessments)	The proportion of participants who were pain-free at 15 minutes for ≥50% of their treated attacks; the proportion of participants who were pain-free or had mild pain at 15 minutes for ≥50% of their treated attacks

Abbreviations: CH, cluster headache; CI, confidence interval; nVNS, non-invasive vagus nerve stimulation.

Table B8: Summary of methodology for the PREVA study

Study name	**PREVA**
Objectives	To assess the efficacy of adjunctive prophylactic nVNS therapy in cCH
Location	10 European sites: 5 in Germany, 3 in the United Kingdom, 1 in Belgium, and 1 in Italy
Design	Prospective, multicentre, open-label, randomised, controlled, parallel-group study
Duration of study	10 weeks (2-week baseline with SoC; 4-week randomised phase of SoC+nVNS or SoC alone; 4-week extension of all patients receiving SoC+nVNS)

Study name	**PREVA**
Sample size	A sample size of 40 participants per treatment arm had 80% power to detect between-group differences in mean change from baseline using a 2-sided test with α≤0.05. An interim analysis of sample size was performed after enrolment of 30 people in each treatment group. Mean reductions in the number of CH attacks per week for SoC+nVNS and control arms were 5.5 and 1.1, respectively (common SD, 6.87); the effect size was 0.65.
Inclusion criteria	Participants were aged 18 to 70 years and were diagnosed with cCH according to ICHD criteria ≥1 year before enrolment
Exclusion criteria	Key exclusion criteria were change in prophylactic medication type or dosage <1 month before enrolment; history of intracranial/carotid aneurysm or haemorrhage; brain tumours/lesions; significant head trauma; previous surgery or abnormal anatomy at the nVNS treatment site; known or suspected cardiac/cardiovascular disease; implantation with electrical or neurostimulation devices; history of carotid endarterectomy or vascular neck surgery; implantation with metallic hardware; and recent history of syncope or seizures.
Method of randomisation	Randomly assigned (1:1) by standard block design to receive SoC+nVNS or SoC alone (control)
Method of blinding	No blinding or masking
Intervention(s) (n=) and comparator(s) (n=)	See Figure B5
Baseline differences	Demographics and baseline characteristics were similar between groups and were representative of the overall CH population; use of SoC prophylactic medications was also comparable between groups
Duration of follow-up, lost to follow-up information	2 weeks (baseline phase); 4 weeks (randomised phase); 4 weeks (extension phase); 7 patients were lost to follow-up (Figure B5); no follow-up after end of study (i.e. open-label phase)
Statistical tests	Analysis of variance and analysis of covariance (site as covariate) were used to assess differences between treatment groups for the primary endpoint and the change in duration and intensity of CH attacks. Within-participant differences in the number of CH attacks and pain intensity ratings reported during the randomised and extension phases were analysed using the Wilcoxon rank sum test. Differences in response rates between treatment groups were evaluated using chi-square analysis without continuity correction. 2-sided *P*-values were calculated, and $P<0.05$ was considered statistically significant.
Primary outcomes (including scoring methods and timing of assessments)	The primary endpoint was the reduction in the mean number of CH attacks per week, defined as the number of attacks during the last 2 weeks of the randomised phase minus the number of attacks during baseline divided by 2. Attack frequency was evaluated during the last 2 weeks of the 4-week randomised phase to ensure sufficient time for nVNS to demonstrate its full effect. Reductions in the mean number of CH attacks per week were also evaluated during the last 2 weeks of the extension phase.
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints included ≥50% response rate (i.e. proportion of participants with ≥50% reduction in mean number of CH attacks per week), abortive medication use, duration and intensity of CH attacks that were acutely treated with nVNS, and safety/tolerability. The ≥50% response rate was assessed during the last 2 weeks of the randomised phase and the last 2 weeks of the extension phase. All other secondary endpoints were assessed at baseline and during the last 2 weeks of the randomised and extension phases. Participant-completed headache diaries captured the number of CH attacks, CH pain intensity (5-point scale: none to very severe), CH duration, and abortive medication use. The EQ-5D-3L and HIT-6 instruments were used to assess QoL at the end of baseline and at the end of both treatment phases. Adherence to nVNS treatment was evaluated in each phase by dividing the actual number of doses administered by the prescribed number of doses.

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; EQ-5D-3L, 3-level version of the EuroQol 5-dimension scale; HIT-6, 6-item Headache Impact Test; ICHD, International Classification of Headache Disorders; nVNS, non-invasive vagus nerve stimulation; QoL, quality of life; SD, standard deviation; SoC, standard of care.

Table B9: Summary of methodology for the Marin et al (2018) study

Study name	**Marin et al (2018)**
Objectives	To retrospectively evaluate data from patients with CH in the United Kingdom who were at various stages of applying for IFRs for nVNS from the National Health Service; to gain further insight into data on nVNS from randomised clinical trials
Location	10 clinical centres throughout the United Kingdom
Design	Retrospective audit of real-world data
Duration of study	3 to 6 months
Patient population	30 patients (29 with cCH and 1 with eCH)
Sample size	No sample size calculation reported
Inclusion criteria	Patients with CH who previously had an inadequate response and/or intolerable side effects with ≥3 current or previous CH treatments and were offered nVNS therapy for use during an evaluation period were eligible for inclusion. Patients who reported a clinically meaningful decrease in the frequency, severity, or duration of their attacks after ≥3 months of evaluation were considered for inclusion in the IFR process. Decreases in the use of concomitant medications and clinical assessments of patient quality of life were also considered. The decision to pursue IFR submission for these subjects was at the discretion of physicians and patients, but submission was not encouraged for patients who did not achieve a ≥25% decrease in weekly attack frequency. Patients continued to use nVNS during IFR development, submission, and processing.
Exclusion criteria	Patients who were no longer experiencing attacks at the time of the analysis were excluded from analyses of attack duration and severity.
Intervention(s) (n=) and comparator(s) (n=)	Physicians instructed patients to use nVNS as preventive therapy, acute treatment, or both. Initial nVNS dosing was based on established paradigms and titrated as necessary to achieve maximum benefit. SoC+nVNS (n=30) vs SoC alone (n=30) (i.e. within-patient changes from baseline)
Baseline differences	N/A; no comparator group at baseline
How were participants followed up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Retrospective follow-up of patients who responded to nVNS in a 3- to 6-month evaluation period
Statistical tests	Attack frequency, duration, and severity were assessed via paired *t* tests. Other data were summarised with descriptive statistics.
Primary outcomes (including scoring methods and timing of assessments)	Primary outcomes were not defined. Attack frequency, duration, and severity (rated on a 0-10 scale; higher numbers indicating greater severity) were the main outcomes of interest.
Secondary outcomes (including scoring methods and timing of assessments)	Secondary outcomes were not defined. Number and timing of stimulations administered, concomitant use of preventive and/or abortive treatments, AEs, and subjective feedback on nVNS were also evaluated.

Abbreviations: AE, adverse event; cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; IFR, individual funding request; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B10: Summary of methodology for the Nesbitt et al (2015) study

Study name	**Nesbitt et al (2015)**
Objectives	To report initial experience with nVNS, both acutely and preventively, as a treatment for CH
Location	2 tertiary headache centres in the United Kingdom
Design	Pilot study; audited experience and clinical efficacy of nVNS
Duration of study	12 months
Patient population	19 patients (8 eCH; 11 cCH)
Sample size	No sample size calculation reported
Inclusion criteria	Patients meeting the current diagnostic criteria of CH: active episodic and chronic.
Exclusion criteria	Clinical judgement led to the exclusion of patients implanted with active neurostimulation devices or cardiac pacemakers or with a significant history of autonomic disorders or cardiac arrhythmia.
Intervention(s) (n=) and comparator(s) (n=)	nVNS was given as an adjunct or first-line treatment (n=19) vs SoC alone (n=19) (i.e. within-patient changes from baseline)
Baseline differences	N/A; no comparator group at baseline
How were participants followed up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Audit of clinical experience with up to 1 year of follow-up
Statistical tests	When a range of values for frequency, attack, or bout duration was provided, the midpoint between the lower and upper values was used. Comparison of frequency data was performed using a general linear model with repeated measures, which additionally assessed group differences between eCH and cCH patients.
Primary outcomes (including scoring methods and timing of assessments)	Primary outcomes were not defined. Patients' percentage estimate of perceived overall change in condition from baseline was the main outcome of interest.
Secondary outcomes (including scoring methods and timing of assessments)	Secondary outcomes were not defined. Percentage change in use of other acute treatments (i.e. high-flow oxygen and parenteral triptans), percentage of attacks treated acutely, proportion of these that were terminated within 15 minutes of initial device use, and time taken to do so were also evaluated

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B11: Summary of methodology for the Trimboli et al (2018) study

Study name	**Trimboli et al (2018)**
Objectives	To evaluate the preventive and abortive effects of nVNS in patients with refractory primary chronic headaches
Location	Headache Centre at Guy's and St Thomas' Hospital, London, UK
Design	Open-label prospective audit in a real-world setting
Duration of study	4 months (>1 month baseline; 3 months nVNS)
Patient population	12 patients with cCH
Sample size	No sample size calculation reported

Study name	**Trimboli et al (2018)**
Inclusion criteria	Patients with refractory headache meeting the IHS criteria for chronic migraine and trigeminal autonomic cephalalgias; the definitions of refractory chronic migraine and cCH were based on EHF recommendations.
Exclusion criteria	Patients with active neurostimulation devices or cardiac pacemakers or with a significant history of cardiac arrhythmia were not offered the treatment.
Intervention(s) (n=) and comparator(s) (n=)	Abortive and preventive nVNS (n=12) vs baseline (n=12) (i.e. within-patient changes from baseline)
Baseline differences	N/A; no comparator group at baseline
How were participants followed-up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Prospective follow-up during the period between January 2014 and August 2016 (>1 month at baseline; nVNS for 3 months)
Statistical tests	N/A; results provided through by-patient listings and descriptive statistics
Primary outcomes (including scoring methods and timing of assessments)	Primary outcomes not defined
Secondary outcomes (including scoring methods and timing of assessments)	Secondary outcomes not defined

Abbreviations: cCH, chronic cluster headache; CH, cluster headache; EHF, European Headache Federation; IHS, International Headache Society; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

7.4.2 Details on data from any single study that have been drawn from more than one source

Additional data obtained from the ACT1 and ACT2 studies were reported in one source beyond the 2 primary publications described in section 7.4.1. The de Coo et al (2019) analysis identified in the unpublished study search is linked to both the ACT1 and ACT2 studies because it reports a pooled analysis of data from these 2 primary publications. This analysis is detailed further in sections 7.4, 7.5, 7.6, and 7.8.

Additional data obtained from the PREVA study were reported in 3 separate sources beyond the primary publication described in section 7.4.1 (Morris et al. 2016, Gaul et al. 2017, Gaul et al. 2018). Data from PREVA were used

along with a pharmacoeconomic model from the German statutory health insurance perspective in a cost-effectiveness analysis of nVNS for patients with cCH (Morris et al. 2016). Use of SoC+nVNS generated greater health benefits for a lower cost than SoC alone, with higher mean quality-adjusted life-years (0.607 vs 0.522) and lower mean expected yearly overall costs (€7096.69 vs €7511.35) and abortive medication costs (€5775.48 vs €7511.35, respectively).

Two post hoc analyses of PREVA data were reported separately in a published article (Gaul et al. 2017) and in unpublished form, the latter is provided as an abstract and poster from the most recent conference at which the analysis was presented (Gaul et al. 2018). Findings of the first post hoc analysis indicated that significant benefits of SoC+nVNS (vs SoC alone) on weekly attack frequency occurred as early as 2 weeks from the start of nVNS use and were sustained through week 3 of the extension phase (P<0.02). Adjunctive nVNS also had significant effects on expanded response rates (vs SoC alone) when *response* was defined as attack frequency reductions of ≥25% (76% vs 23%; P<0.001), ≥50% (49% vs 9%; P<0.001), and ≥75% (22% vs 2%; P=0.009), with 100% response rates of 8% with SoC+nVNS vs 0% with SoC alone. In the second post hoc analysis, patients who used acute nVNS treatment more frequently (i.e. for ≥76.9% of their attacks; n=22) had a significantly better response vs SoC alone (–8.5 vs –2.1 attacks/week; P<0.01), whereas those who used acute nVNS less frequently (i.e. for <76.9% of their attacks; n=22) did not have a significantly better response vs SoC alone (–3.7 vs –2.1 attacks/week; P=1.00).

7.4.3 Differences between patient populations and methodology in all included studies

The ACT1, ACT2, and Nesbitt et al (2015) studies comprised both eCH and cCH patient populations, with ACT1 having more eCH patients (n=101) than cCH patients (n=49), and with the ACT2 and Nesbitt et al (2015) studies having more cCH patients (ACT2, n=72; Nesbitt et al [2015], n=11) than eCH patients (ACT2, n=30; Nesbitt et al [2015], n=8). The ACT1 study was conducted in the United States, whereas the ACT2 and Nesbitt et al (2015)

studies were conducted in the European Union. ACT1 and ACT2 were randomised, double-blind, sham-controlled trials, whereas the Nesbitt et al (2015) study was observational. All 3 of these studies evaluated abortive use of nVNS, and the Nesbitt et al (2015) study also evaluated preventive use. The acute stimulation protocol used was three 120-second stimulations per attack in all 3 studies, with ACT2 allowing for an additional 3 stimulations if the attack was not aborted within 9 minutes of treatment initiation. The side of stimulation also differed among the studies (ACT1, right side; ACT2 and Nesbitt et al [2015], ipsilateral to the attack). A maximum of 2 and 4 attacks could be treated per day in ACT1 and ACT2 double-blind periods, respectively, with no maximum specified in the Nesbitt et al (2015) publication.

In the PREVA, Marin et al (2018), and Trimboli et al (2018) studies, almost all CH patients had cCH (PREVA, n=97; Marin et al [2018], n=29; Trimboli et al [2018], n=12), with only 1 patient having eCH in the Marin et al (2018) study. PREVA was a randomised, open-label, controlled trial, whereas the Marin et al (2018) and Trimboli et al (2018) studies were clinical audits of real-world data. All 3 of these studies were conducted in the European Union and evaluated both abortive and preventive use of nVNS. The Trimboli et al (2018) study used 90-second stimulations rather than 120-second stimulations. The abortive stimulation protocols were otherwise consistent with those used in the eCH/cCH studies above (i.e. 3 consecutive stimulations at attack onset). The preventive stimulation protocols used were 3 stimulations administered twice daily in PREVA and 2 stimulations administered 3 times daily in the Trimboli et al (2018) study, with both protocols used in the Marin et al (2018) study. The side of stimulation also differed among the studies (PREVA, right side; Marin et al [2018], ipsilateral to the pain, when possible; Trimboli et al [2018], any side or alternating sides).

7.4.4 Details of subgroup analyses that were undertaken in the studies included in section 7.4.1 (rationale and prespecified/post hoc)

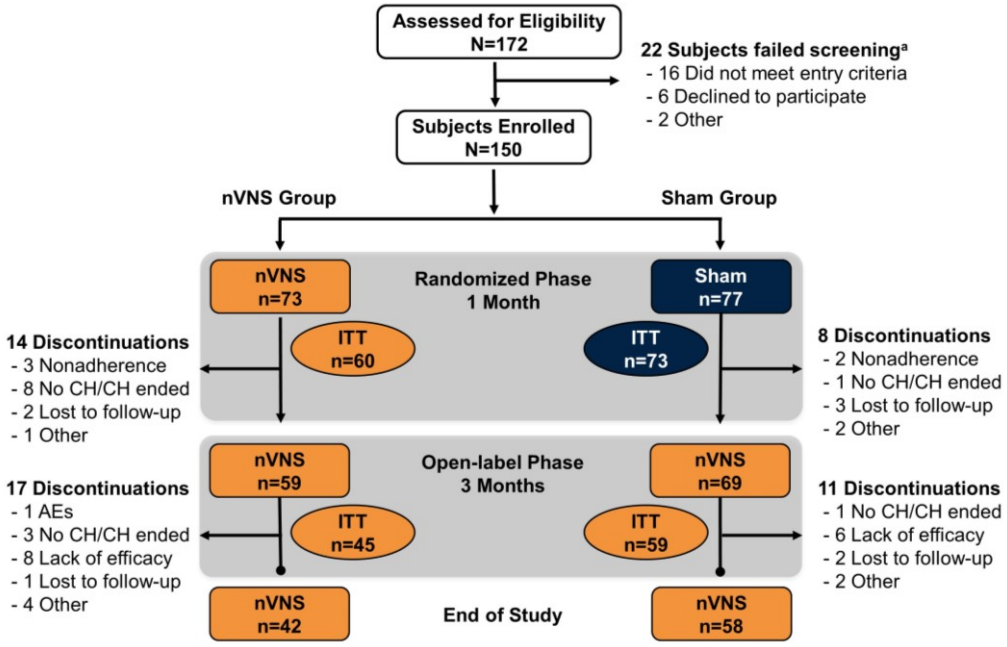
Efficacy analyses of eCH and cCH cohorts were prespecified for the ACT1, ACT2, and de Coo et al (2019) studies, with the rationale being that these CH subtypes have distinct ICHD clinical definitions and may have differential

responses to acute treatment (Headache Classification Committee of the International Headache Society. 2018, Lipton et al. 1995). Findings from these analyses are provided in section 7.6.

7.4.5 Details of the numbers of patients who were enrolled, randomised, and allocated to each treatment

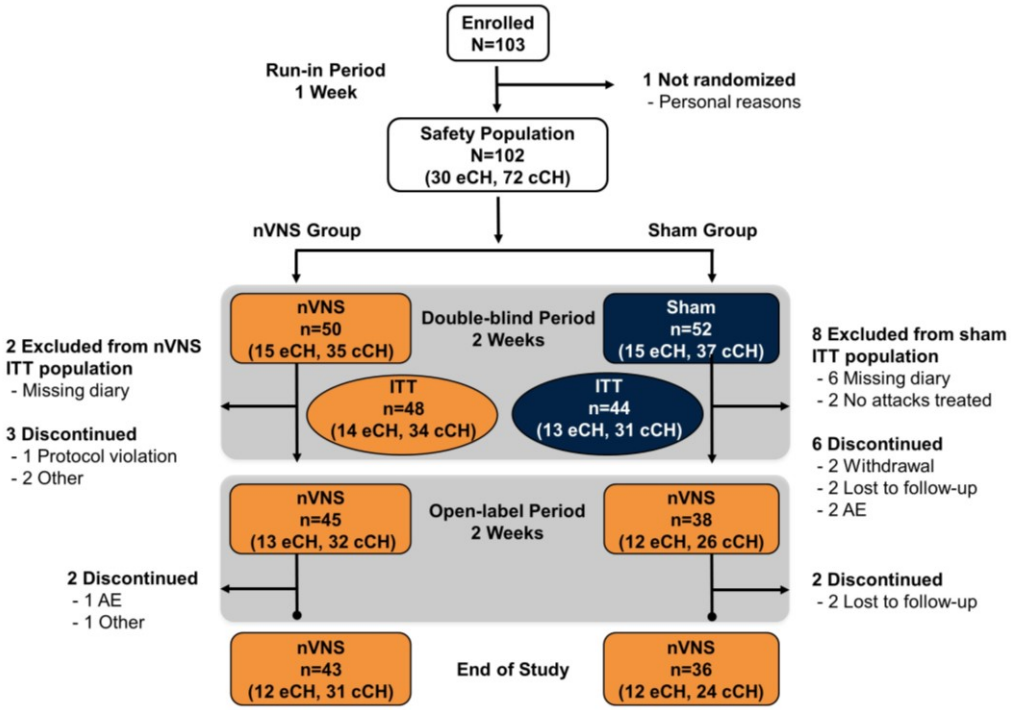
For the ACT1, ACT2, PREVA, and Nesbitt et al (2015) studies identified in section 7.3, details on patient disposition, including patients who were enrolled, randomised, and allocated to treatment, as well as reasons for study discontinuation, are provided below in the flow charts (Figure B3, Figure B4, Figure B5, and Figure B6). Patient disposition for the de Coo et al (2019) study is represented by both Figure B3 and Figure B4. The Marin et al (2018) and Trimboli et al (2018) studies were clinical audits of real-world data, with no randomisation or comparator group. The Marin et al (2018) study retrospectively evaluated all 30 enrolled patients with cluster headache (29 chronic cluster headache; 1 episodic cluster headache) who received nVNS, with no reported study withdrawals or patients lost to follow-up. Patients who lacked quantitative attack duration or severity data or were no longer having attacks were excluded at the time of quantitative analysis of these outcomes. For the Trimboli et al (2018) study, the 12 patients with chronic cluster headache who received nVNS are reported on here. (This study also evaluated 23 patients with chronic migraine, 4 patients with hemicranias continua, and 2 patients with short-lasting unilateral neuralgiform headache attacks with autonomic symptoms [SUNA].) One patient with chronic cluster headache discontinued nVNS treatment because of a worsening of his or her condition for 3 consecutive months after receiving the therapy for 10 months.

Figure B3: ACT1 CONSORT flow chart



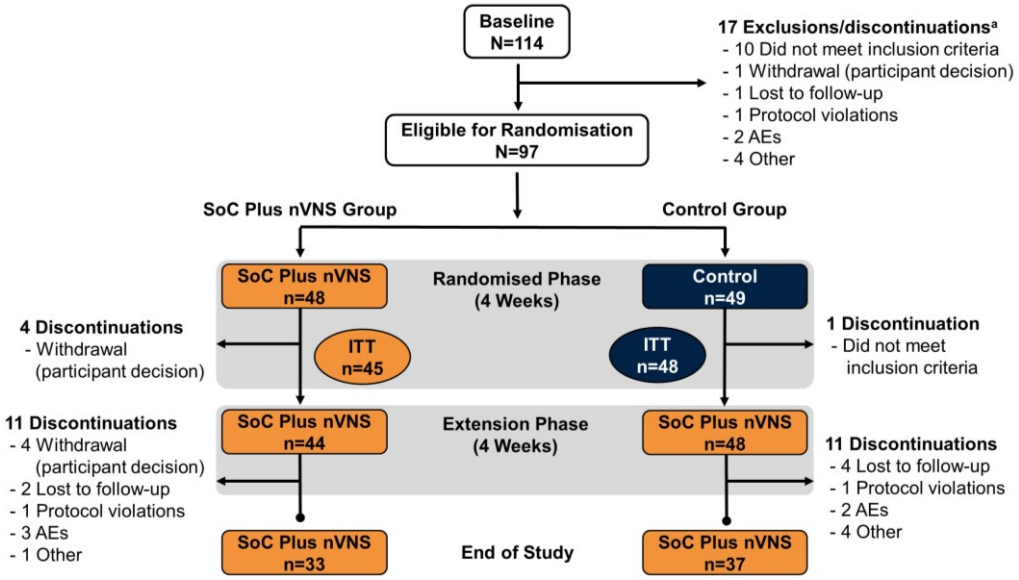
[a] Some subjects failed screening for >1 reason.
Abbreviations: AE, adverse event; CH, cluster headache; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Figure B4: ACT2 CONSORT flow chart



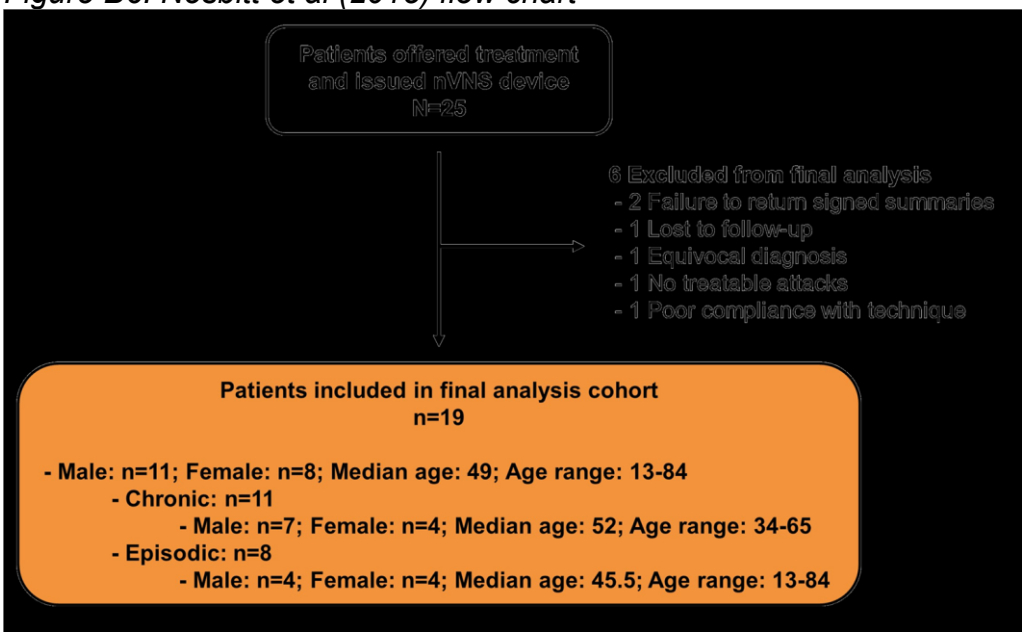
Abbreviations: AE, adverse event; cCH, chronic cluster headache; eCH, episodic cluster headache; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Figure B5: PREVA CONSORT flow chart



[a] Exclusions or discontinuations for more than 1 reason occurred in some subjects.
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Figure B6: Nesbitt et al (2015) flow chart



Abbreviation: nVNS, non-invasive vagus nerve stimulation.

7.4.6 Details of and the rationale for patients who were lost to follow-up or withdrew from the studies

All reasons for patient withdrawals from the studies are provided in section 7.4.5.

7.5 Critical appraisal of relevant studies

7.5.1 Quality assessment tables for each study

Table B12: Critical appraisal of the ACT1 study

Study name	**ACT1**	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Independent statistician–generated randomisation schedules were used to assign subjects (1:1 allocation) to receive nVNS or sham treatment using a variable block design stratified by study site.
Was the concealment of treatment allocation adequate?	Yes	Devices were labelled with randomisation numbers and allocated to study sites by a third-party distributor according to the randomisation scheme.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline characteristics were similar between groups and were consistent with those of a typical CH patient population.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Missing data were imputed as failures for response variables and using the last observation carried forward for attack intensity.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviations: CH, cluster headache; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B13: Critical appraisal of the ACT2 study

Study name	**ACT2**	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	A standard design with a block size of 4 was used to randomly assign subjects (in a 1:1 ratio) to receive treatment with either nVNS or the sham device.

Study name	ACT2	
Study question	**Response**	**How is the question addressed in the study?**
Was the concealment of treatment allocation adequate?	Yes	Each study site received sealed randomisation envelopes imprinted with subject numbers; subjects were enrolled in consecutive order at each site.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	The mean duration of attacks and median number of attacks per week during the run-in period were similar between treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Subjects were included in the analyses for all endpoints for which they provided data.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B14: Critical appraisal of the de Coo et al (2019) study

Study name	de Coo et al (2019)	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	This is a pooled analysis of studies described in Table B12 and Table B13; randomisation is detailed in the original articles.
Was the concealment of treatment allocation adequate?	Yes	This is a pooled analysis of studies described in Table B12 and Table B13; concealment is detailed in the original articles.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	This is a pooled analysis of studies described in Table B12 and Table B13; baseline patient characteristics are detailed in the original articles.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	This is a pooled analysis of studies described in Table B12 and Table B13; blinding is detailed in the original articles.

Study name	de Coo et al (2019)	
Study question	**Response**	**How is the question addressed in the study?**
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	This is a pooled analysis of studies described in Table B12 and Table B13; drop-outs are detailed in the original articles.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Methods of accounting for missing data are identified in source studies.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviation: N/A, not applicable.

Table B15: Critical appraisal of the PREVA study

Study name	PREVA	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Subjects were randomly assigned (1:1 allocation) using a standard block design to receive either SoC plus nVNS or SoC alone.
Was the concealment of treatment allocation adequate?	N/A	Open-label study
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Disease characteristics at baseline were similar between treatment groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Possible placebo response to nVNS
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	

Study name	PREVA	
Study question	**Response**	**How is the question addressed in the study?**
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Missing data were imputed to *no change* for reduction in the number of CH attacks or to *no response* for response rate.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, United Kingdom: Centre for Reviews and Dissemination.
Abbreviations: CH, cluster headache; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B16: Critical appraisal of the Marin et al (2018) study

Study name	Marin et al (2018)	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Not clear	Data from 30 patients who submitted individual funding requests for nVNS to the National Health Service were retrospectively analysed. Site recruitment methodology is unclear. Selection bias owing to the inclusion of only patients who responded to nVNS is acknowledged.
Was the exposure accurately measured to minimise bias?	Yes	
Was the outcome accurately measured to minimise bias?	Yes	
Have the authors identified all important confounding factors?	Not clear	Potential confounding factors are not addressed.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	In the discussion section, the authors accounted for inclusion bias (inherent in a responder analysis) as a limitation.
Was the follow-up of patients complete?	N/A	Retrospective review
How precise (for example, in terms of confidence interval and *P*-values) are the results?	Moderate	Sample size is small; standard deviations are large.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence─12 questions to help you make sense of a cohort study.
Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B17: Critical appraisal of the Nesbitt et al (2015) study

Study name	Nesbitt et al (2015)	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Patients from 1 of 2 tertiary headache centres who met the diagnostic criteria for CH (and who did not have implanted active neurostimulation devices, cardiac pacemakers, or significant history of autonomic disorders or cardiac arrhythmia) were treated with adjunctive or first-line nVNS.
Was the exposure accurately measured to minimise bias?	Not clear	Data on the number of stimulations used per patient are not reported.

Study name	Nesbitt et al (2015)	
Study question	**Response**	**How is the question addressed in the study?**
Was the outcome accurately measured to minimise bias?	No	Patient estimates (recall data) were used for several outcomes.
Have the authors identified all important confounding factors?	Not clear	Changes in other treatments are identified as a potential confounding factor. No other potential confounding factors are acknowledged.
Have the authors taken account of the confounding factors in the design and/or analysis?	No	
Was the follow-up of patients complete?	Yes	The methods section states that patients were routinely followed up.
How precise (for example, in terms of confidence interval and *P*-values) are the results?	Low precision	Sample size is small; standard errors are large.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence—12 questions to help you make sense of a cohort study.
Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation.

Table B18: Critical appraisal of the Trimboli et al (2018) study

Study name	Trimboli et al (2018)	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Consecutive patients with medically refractory CH from a single centre were included.
Was the exposure accurately measured to minimise bias?	Not clear	Data on the number of stimulations used per patient are not reported.
Was the outcome accurately measured to minimise bias?	Yes	Headache diaries specifically designed for CH were used for data collection.
Have the authors identified all important confounding factors?	Not clear	Potential confounding factors are not addressed.
Have the authors taken account of the confounding factors in the design and/or analysis?	Not clear	Potential confounding factors are not addressed.
Was the follow-up of patients complete?	Not clear	All cCH patients completed the 3-month follow-up, but timing/completion of follow-up visits for the 1 cCH patient who continued nVNS beyond 3 months was not clear.
How precise (for example, in terms of confidence interval and *P*-values) are the results?	Low precision	Sample size is small; no statistical analyses were performed.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence—12 questions to help you make sense of a cohort study.
Abbreviations: cCH, chronic cluster headache; CH, cluster headache.

7.6 Results of the relevant studies

7.6.1 Results tables for each study

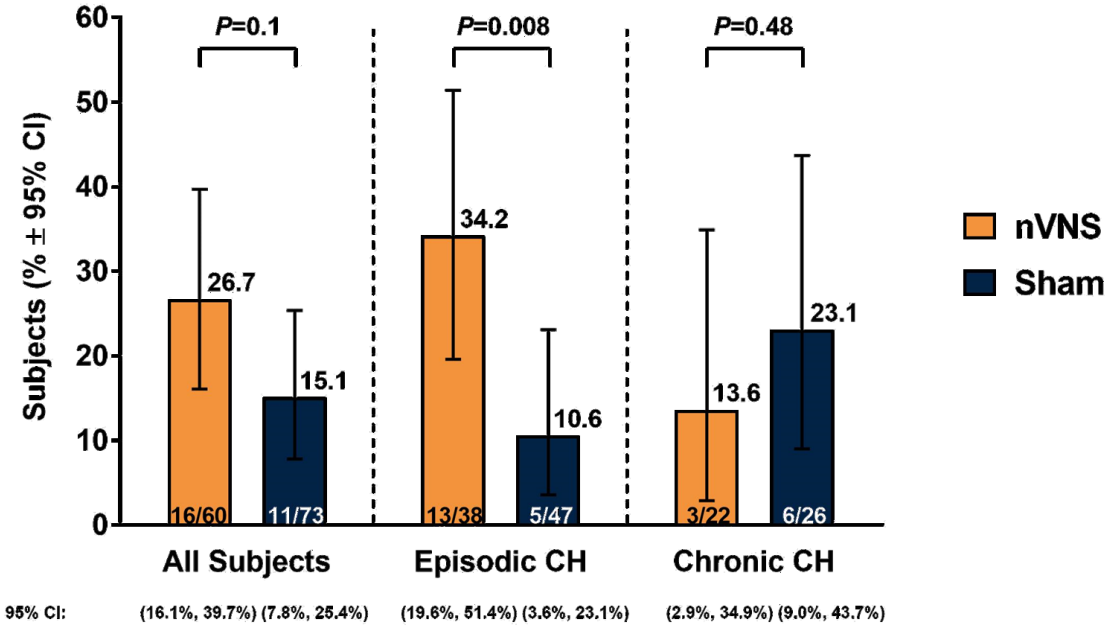
Table B19: Outcomes from the ACT1 study

Study name		**ACT1**
Size of study groups	**Treatment**	n=60 (nVNS; ITT population of double-blind phase)[a]
	Control	n=73 (sham; ITT population of double-blind phase)[a]
Study duration	**Time unit**	Approximately 4 months (double-blind phase, 1 month or 5 treated CH attacks; open-label phase, 3 months)
Type of analysis	**ITT/per-protocol**	ITT
Primary outcome	**Name**	Response rates (prespecified primary endpoint; total population and eCH and cCH cohorts prespecified)
	Unit	Proportion of all subjects with pain relief at 15 minutes after treatment initiation for the first CH attack[b]
Effect size	**Value**	Total population: Δ=11.6% nVNS: 16/60 subjects (26.7%) Sham: 11/73 subjects (15.1%) eCH cohort: Δ=23.6% nVNS: 13/38 subjects (34.2%) Sham: 5/47 subjects (10.6%) cCH cohort: Δ=–9.5% nVNS: 3/22 subjects (13.6%) Sham: 6/26 subjects (23.1%) Please also see Figure B7 below
	95% CI	Total population: nVNS: (16.1%, 39.7%) Sham: (7.8%, 25.4%) eCH cohort: nVNS: (19.6%, 51.4%) Sham: (3.6%, 23.1%) cCH cohort: nVNS: (2.9%, 34.9%) Sham: (9.0%, 43.7%)
Statistical test	**Type**	Fisher's exact test (if ≥1 cell had an expected frequency of ≤5) or the chi-square test[c]
	***P*-value**	Total population (nVNS vs sham): *P*=0.1 eCH (nVNS vs sham): *P*=0.008 cCH (nVNS vs sham): *P*=0.48
Secondary outcome	**Name**	Sustained pain response (prespecified secondary endpoint; subanalyses of eCH and cCH cohorts were also prespecified)
	Unit	Proportion of subjects with pain relief without rescue medication at 15 minutes through 60 minutes
Effect size	**Value**	Total population: Δ=14.4% nVNS: 16/60 subjects (26.7%) Sham: 9/73 subjects (12.3%) eCH cohort: Δ=23.6% nVNS: 13/38 subjects (34.2%) Sham: 5/47 subjects (10.6%) cCH cohort: Δ=–1.8% nVNS: 3/22 subjects (13.6%) Sham: 4/26 subjects (15.4%)

Study name		ACT1
	95% CI	Total population: nVNS: (16.1%, 39.7%) Sham: (5.8%, 22.1%) eCH cohort: nVNS: (19.6%, 51.4%) Sham: (3.6%, 23.1%) cCH cohort: nVNS: (2.9%, 34.9%) Sham: (4.4%, 34.9%)
Statistical test	**Type**	Fisher's exact test (if ≥1 cell had an expected frequency of ≤5) or the chi-square test[c]
	***P*-value**	Total population (nVNS vs sham): *P*=0.04 eCH (nVNS vs sham): *P*=0.008 cCH (nVNS vs sham): *P*=1.0

Comments: [a] Details on power of the study and sample size calculations are provided in Table B5.
[b] Consistent with the IHS-recommended primary efficacy outcome for acute CH therapy (Lipton et al. 1995).
[c] Missing data were imputed as failures; subjects with missing data at any time point(s) for rescue medication use (i.e. 15, 30, and/or 60 minutes) were considered nonresponders.
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; IHS, International Headache Society; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Figure B7: Response rates at 15 minutes in the ACT1 study



Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation.

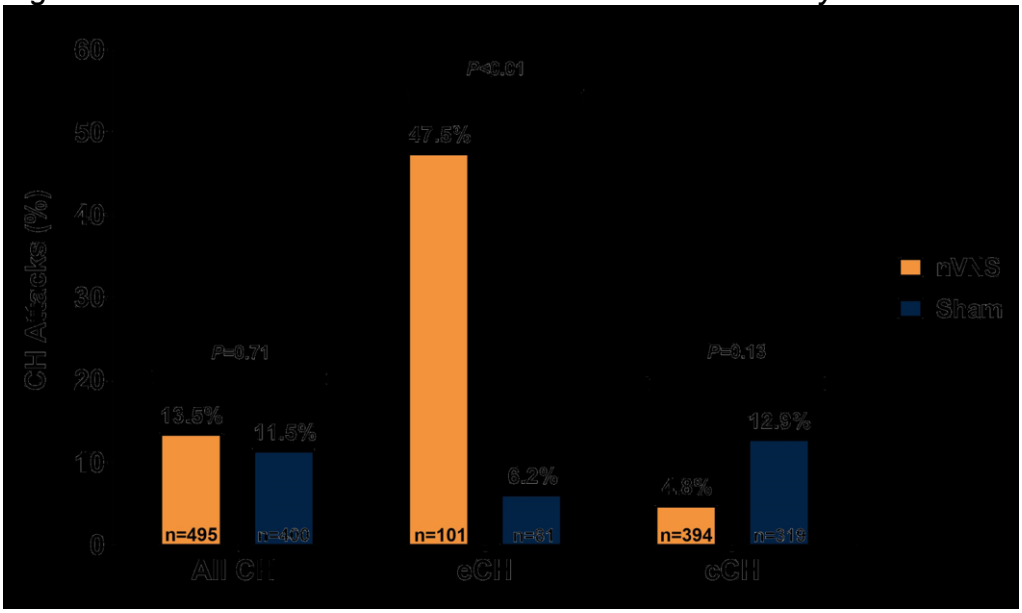
Table B20: Outcomes from the ACT2 study

Study name		ACT2
Size of study groups	**Treatment**	n=48 (nVNS; ITT population of double-blind period)[a]
	Control	n=44 (sham device; ITT population of double-blind period)[a]
Study duration	**Time unit**	5 weeks (run-in period, 1 week; double-blind period, 2 weeks; open-label period, 2 weeks)
Type of analysis	**ITT/per-protocol**	ITT
Primary outcome	**Name**	Pain-free rates (total population and eCH and cCH cohorts prespecified)
	Unit	Proportion of all treated attacks with pain-free status within 15 minutes after treatment initiation[b]
Effect size	**Value**	Total population: Δ=2.0% nVNS: 67/495 attacks (13.5%) Sham: 46/400 attacks (11.5%) eCH: Δ=41.3% nVNS: 48/101 attacks (47.5%) Sham: 5/81 attacks (6.2%) cCH: Δ=–8.1% nVNS: 19/394 attacks (4.8%) Sham: 41/319 attacks (12.9%) Please also see Figure B8
	95% CI	OR (95% CI; OR>1 favours nVNS) Total population: OR=1.22 (0.42, 3.51) eCH: OR=9.19 (1.77, 47.80) cCH: OR=0.41 (0.13, 1.30)
Statistical test	**Type**	Generalised estimating equations model, which was adjusted for site in the total cohort and cCH subgroups but was not adjusted for site in the eCH subgroup was used for analysis.
	***P*-value**	Total population (nVNS vs sham): P=0.71 eCH (nVNS vs sham): P<0.01 cCH (nVNS vs sham): P=0.13
	Type	A type 3 test of fixed effects was conducted to evaluate the interaction between treatment group and CH type.[c]
	***P*-value**	Interaction (treatment group and CH type): P=0.04
Secondary outcome	**Name**	Responder: pain relief
	Unit	Proportion of treated attacks per subject that achieved responder status (i.e. pain score of 0 or 1) within 30 minutes
Effect size	**Value**	Total population: Δ=15.1% nVNS: 42.7% Sham: 27.6% eCH: Δ=32.0% nVNS: 57.5% Sham: 25.5% cCH: Δ=8.1% nVNS: 36.6% Sham: 28.5%
	SE between treatment groups	Total population: ±7.3% eCH: ±15.0% cCH: ±8.1%

Study name		ACT2
Statistical test	**Type**	Wilcoxon rank sum test stratified by study site[c]
	***P*-value**	Total population: *P*=0.05 eCH: *P*=0.07 cCH: *P*=0.34
Secondary outcome	**Name**	Pain free within 30 minutes
	Unit	Proportion of treated attacks per subject that achieved pain-free status (i.e. pain score of 0)
Effect size	**Value**	Total population: Δ=7.8% nVNS: 26.1% Sham: 18.3% eCH: Δ=23.9% nVNS: 43.0% Sham: 19.1% cCH: Δ=1.3% nVNS: 19.2% Sham: 17.9%
	SE between treatment groups	Total population: ±6.4% eCH: ±14.4% cCH: ±6.5%
Statistical test	**Type**	Wilcoxon rank sum test stratified by study site[c]
	***P*-value**	Total population: *P*=0.17 eCH: *P*=0.08 cCH: *P*=0.76

Comments: [a] Details on power of the study and sample size calculations are provided in Table B6.
[b] Consistent with the IHS-recommended primary efficacy outcome for acute CH therapy (Lipton et al. 1995).
[c] If rescue treatment was used at any point after initiation of stimulation for an attack, that attack was counted as a treatment failure; no outliers were identified; data from prematurely withdrawn subjects were included in the analyses to the extent possible.
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; IHS, International Headache Society; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; OR, odds ratio; SE, standard error.

Figure B8: Pain-free rates at 15 minutes in the ACT2 study



Abbreviations: cCH, chronic cluster headache; CH, cluster headache; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation.

Table B21: Outcomes from the de Coo et al (2019) study

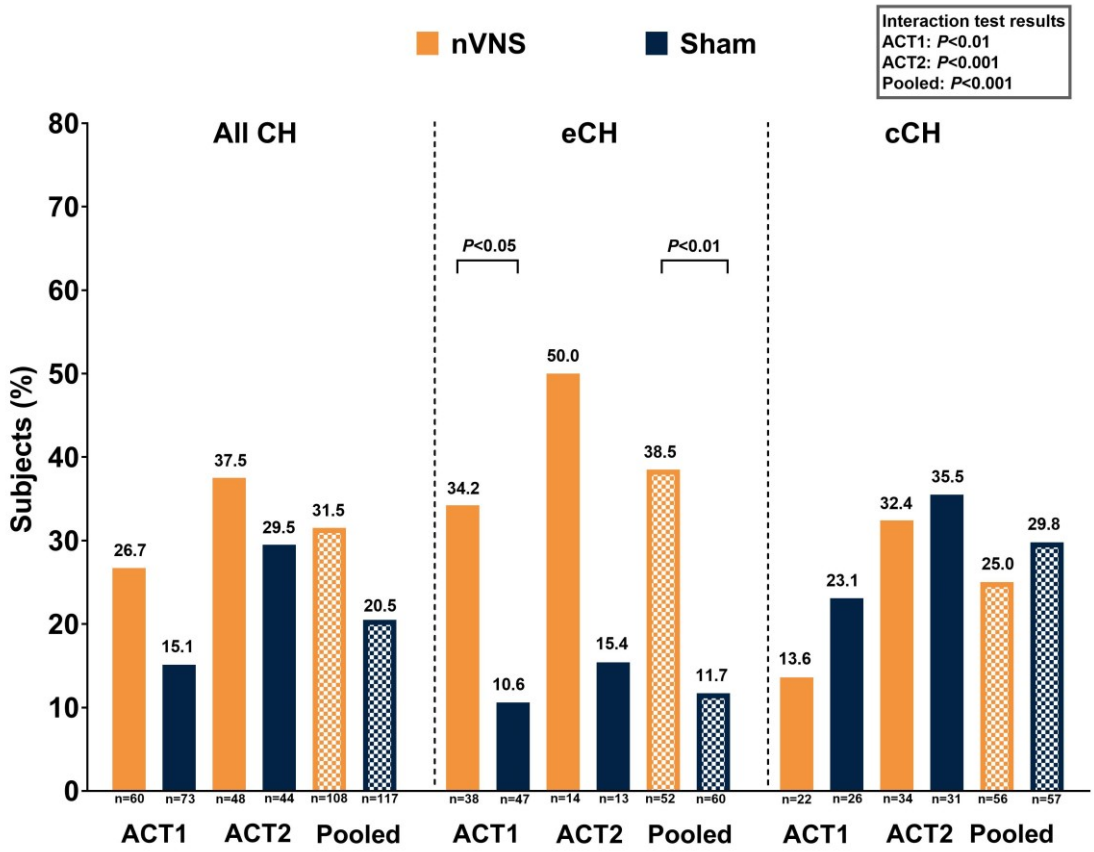
Study name		**de Coo et al (2019)**	
Size of study groups	**Treatment**	n=108 (nVNS; ITT populations pooled from ACT1 and ACT2 double-blind periods)[a]	
	Control	n=117 (sham; ITT populations pooled from ACT1 and ACT2 double-blind periods)[a]	
Study duration	**Time unit**	ACT1: 4 months (1-month double-blind phase; 3-month open-label phase) ACT2: 5 weeks (1-week run-in period; 2-week double-blind period; 2-week open-label period)	
Type of analysis	**ITT/per-protocol**	ITT	
Primary outcome	**Name**	Treatment response at 15 minutes in first treated attack (ACT1 primary efficacy endpoint)[b]	
	Unit	OR	
Effect size	**Value**	All CH OR ACT1: 2.05 ACT2: 1.43 Pooled: 1.72 eCH OR ACT1: 4.37 ACT2: 5.50 Pooled: 4.67 cCH OR ACT1: 0.53 ACT2: 0.87 Pooled: 0.74 Please also see Figure B9 below	All CH absolute difference ACT1: nVNS, 16/60; sham, 11/73 26.7% – 15.1% = 11.6% ACT2: nVNS, 18/48; sham, 13/44 37.5% – 29.5% = 8.0% Pooled: nVNS, 34/108; sham, 24/117 31.5% – 20.5% = 11.5% eCH absolute difference ACT1: nVNS, 13/38; sham, 5/47 34.2% – 10.6% = 23.6% ACT2: nVNS, 7/14; sham, 2/13 50.0% – 15.4% = 34.6% Pooled: nVNS, 20/52; sham, 7/60 38.5% – 11.7% = 26.8% cCH absolute difference ACT1: nVNS, 3/22; sham, 6/26 13.6% – 23.1% = –9.5% ACT2: nVNS, 11/34; sham, 11/31 32.4% – 35.5% = –3.1% Pooled: nVNS, 14/56; sham, 17/57 25.0% – 29.8% = –4.8%
	95% CI	All CH OR CIs ACT1: (0.87, 4.84) ACT2: (0.60, 3.42) Pooled: (0.93, 3.17) eCH OR CIs ACT1: (1.39, 13.71) ACT2: (0.88, 34.46) Pooled: (1.77, 12.32) cCH OR CIs ACT1: (0.12, 2.41) ACT2: (0.31, 2.43) Pooled: (0.32, 1.72)	

Study name		de Coo et al (2019)
Statistical test	**Type**	Logistic regression models to estimate ORs and 95% CIs
	***P*-value**	All CH: ACT1: *P*=0.10 ACT2: *P*=0.42 Pooled: *P*=0.08 eCH: ACT1: *P*=0.01 ACT2: *P*=0.07 Pooled: *P*<0.01 cCH: ACT1: *P*=0.41 ACT2: *P*=0.79 Pooled: *P*=0.48
	Type	First-order interactions between treatment group and CH type were examined to determine whether magnitude of treatment effect varied significantly by CH type.
	***P*-value**	ACT1: *P*<0.01 ACT2: *P*<0.001 Pooled: *P*<0.001
Primary outcome	**Name**	Proportion of all attacks that were pain-free at 15 minutes (ACT2 primary efficacy endpoint)[b]
	Unit	Percentage
Effect size	**Value**	All CH GEE model adjustment difference ACT1: nVNS, 28/259; sham, 26/319 11.52% – 8.40% = 3.12% ACT2: nVNS, 67/495; sham, 46/400 14.96% – 8.66% = 6.3% Pooled: nVNS, 95/754; sham, 72/719 13.16% – 8.68% = 4.48% eCH GEE model adjustment difference ACT1: nVNS, 24/158; sham, 13/206 15.44% – 6.09% = 9.35% ACT2: nVNS, 48/101; sham, 5/81 35.18% – 7.41% = 27.77% Pooled: nVNS, 72/259; sham, 18/287 24.05% – 7.34% = 16.71% cCH GEE model adjustment difference ACT1: nVNS, 4/101; sham, 13/113 5.29% – 14.56% = –9.27% ACT2: nVNS, 19/394; sham, 41/319 7.41% – 9.22% = –1.81% Pooled: nVNS, 23/495; sham, 54/432 6.75% – 10.94% = –4.19% Please also see Figure B10 below

Study name		de Coo et al (2019)
	95% CI	All CH CIs ACT1: nVNS (7.00, 18.38); sham (4.92, 13.96) ACT2: nVNS (9.01, 23.82); sham (4.24, 16.86) Pooled: nVNS (9.28, 18.35); sham (5.66, 13.08) eCH CIs ACT1: nVNS (9.49, 24.12); sham (3.00, 11.96) ACT2: nVNS (19.12, 55.48); sham (1.59, 28.44) Pooled: nVNS (16.68, 33.38); sham (3.75, 13.89) cCH CIs ACT1: nVNS (1.06, 22.49); sham (6.07, 31.00) ACT2: nVNS (3.28, 15.89); sham (4.33, 18.57) Pooled: nVNS (3.28, 13.39); sham (6.30, 18.33)
Statistical test	**Type**	Generalised linear mixed-effects regression models were used to estimate the proportion of all treated attacks. *P*-values are from *F* tests.
	***P*-value**	All CH: ACT1: *P*=0.38 ACT2: *P*=0.20 Pooled: *P*=0.13 eCH: ACT1: *P*=0.03 ACT2: *P*=0.04 Pooled: *P*<0.01 cCH: ACT1: *P*=0.25 ACT2: *P*=0.69 Pooled: *P*=0.28
	Type	First-order interactions between treatment group and CH type were examined to determine whether magnitude of treatment effect varied significantly by CH type.
	***P*-value**	ACT1: *P*=0.03 ACT2: *P*=0.04 Pooled: *P*<0.01

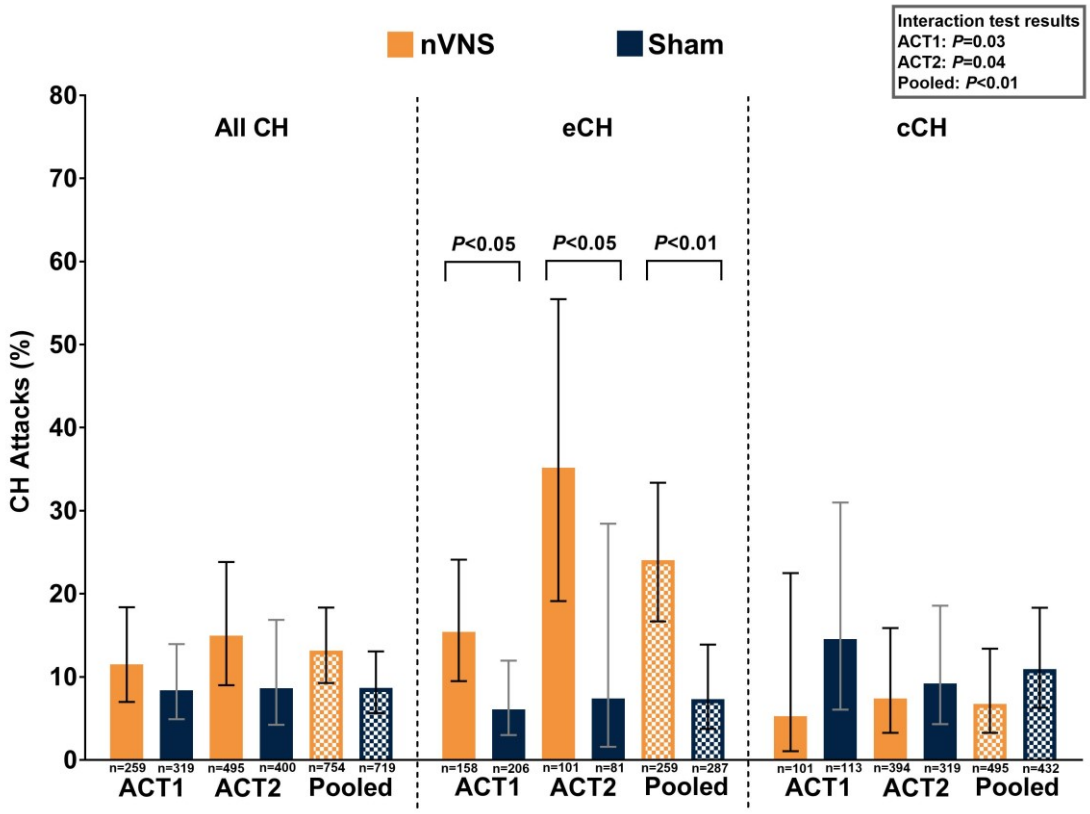
Comments: [a] Details on power of the studies and sample size calculations are provided in Table B5 and Table B6.
[b] Consistent with the IHS-recommended primary efficacy outcome for acute CH therapy (Lipton et al. 1995).
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; GEE, generalised estimating equation; IHS, International Headache Society; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; OR, odds ratio.

Figure B9: Response rates in the de Coo et al (2019) study (ACT1 primary endpoint)



Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; OR, odds ratio.

Figure B10: Pain-free rates in the de Coo et al (2019) study (ACT2 primary endpoint)



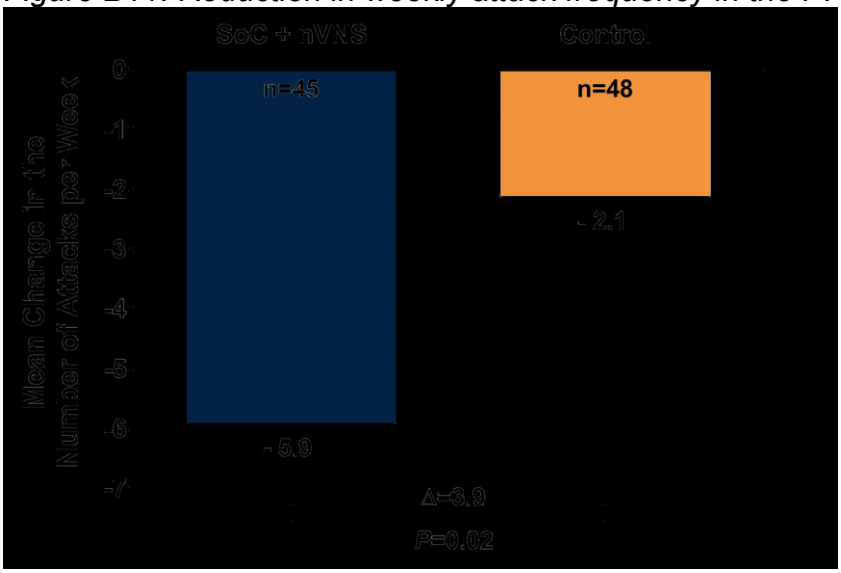
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulation; OR, odds ratio.

Table B22: Outcomes from the PREVA study

Study name		PREVA
Size of study groups	**Treatment**	n=45 (SoC+nVNS; ITT population of randomised phase)[a]
	Control	n=48 (SoC alone; ITT population of randomised phase)[a]
Study duration	**Time unit**	10 weeks (baseline phase, 2 weeks; randomised phase, 4 weeks; optional extension phase, 4 weeks)
Type of analysis	**ITT/per-protocol**	ITT
Primary outcome	**Name**	Change in CH attack frequency per week
	Unit	Change in mean number of CH attacks per week (baseline to last 2 weeks of randomised phase)[b]
Effect size	**Value**	Difference between groups: Δ=3.9 SoC+nVNS: –5.9 SoC alone: –2.1 Please also see Figure B11 below
	Standard error	SoC+nVNS: ±1.2 SoC alone: ±1.2
	95% CI	Therapeutic gain: (0.5, 7.2)
Statistical test	**Type**	Analysis of variance[c]
	***P*-value**	*P*=0.02
Secondary outcome	**Name**	≥50% response rate
	Unit	Proportion of participants with ≥50% reduction in mean number of CH attacks per week
Effect size	**Value**	SoC+nVNS: 18/45 (40%) SoC alone: 4/48 (8.3%)
	95% CI	Not reported
Statistical test	**Type**	Chi-square analysis without continuity correction[d]
	***P*-value**	*P*<0.001

Comments: [a] Details on power of the study and sample size calculations are provided in Table B8.
[b] Consistent with the IHS-recommended primary efficacy outcome for preventive CH therapy (Lipton et al. 1995).
[c] Missing data were imputed to 0 (i.e. no change; designated as treatment failures).
[d] Missing data were imputed to no response.
Abbreviations: CH, cluster headache; CI, confidence interval; IHS, International Headache Society; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Figure B11: Reduction in weekly attack frequency in the PREVA study



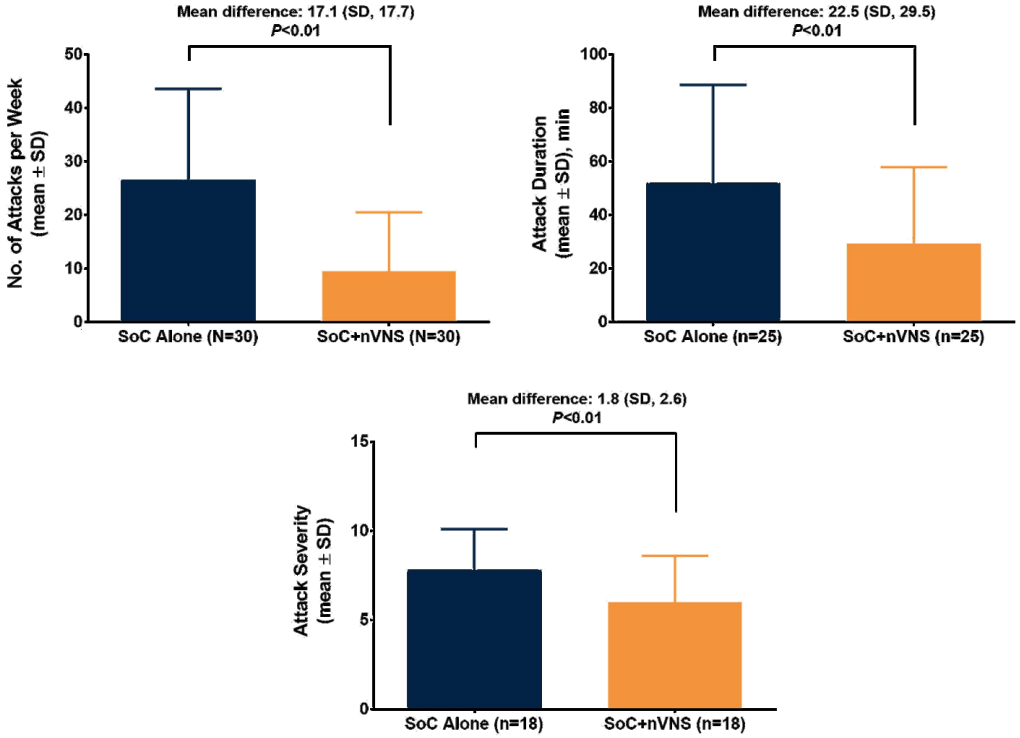
Abbreviations: CH, cluster headache; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B23: Outcomes from the Marin et al (2018) study

Study name		**Marin et al (2018)**
Size of study groups	**Treatment**	n=30 (SoC+nVNS; cCH, n=29; eCH, n=1)
	Control	n=30 (SoC alone; within-patient baseline control; cCH, n=29; eCH, n=1)
Study duration	**Time unit**	3 to 6 months
Type of analysis	**ITT/per-protocol**	N/A
Outcome	**Name**	Mean attack frequency (n=30)
	Unit	Mean change in CH attack frequency per week[a]
Effect size	**Value**	Mean difference: 17.1 attacks per week SoC alone: 26.6 attacks per week SoC+nVNS: 9.5 attacks per week Please also see Figure B12 below
	SD	Mean difference SD: ±17.7
	Range	SoC alone: 3.8 to 77.0 attacks per week SoC+nVNS: 0 to 38.5 attacks per week
Statistical test	**Type**	Paired *t* tests
	***P*-value**	*P*<0.01
Outcome	**Name**	Mean attack duration (n=25)
	Unit	Minutes
Effect size	**Value**	Mean difference: 22.5 minutes SoC alone: 51.9 minutes SoC+nVNS: 29.4 minutes Please also see Figure B12 below
	SD	Mean difference SD: ±29.5
	Range	SoC alone: 5.0 to 140.0 minutes SoC+nVNS: 2.5 to 152.5 minutes
Statistical test	**Type**	Paired *t* tests[b]
	***P*-value**	*P*<0.01
Outcome	**Name**	Mean attack severity (n=18)
	Unit	Rated on a 0 to 10 scale (higher numbers indicating greater severity)
Effect size	**Value**	Mean difference: 1.8 SoC alone: 7.8 SoC+nVNS: 6.0 Please also see Figure B12 below
	SD	Mean difference SD: ±2.6
	Range	SoC alone: 3.0 to 10.0 SoC+nVNS: 1.0 to 10.0
Statistical test	**Type**	Paired *t* tests[b]
	***P*-value**	*P*<0.01

Comments: [a] Consistent with the IHS-recommended primary efficacy outcome for preventive CH therapy (Lipton et al. 1995).
[b] Patients who lacked quantitative attack duration or severity data or were no longer having attacks at the time of quantitative analysis of these outcomes were excluded.
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; IHS, International Headache Society; ITT, intent-to-treat; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SD, standard deviation; SoC, standard of care.

Figure B12: Attack frequency, duration, and severity in the Marin et al (2018) study



Abbreviations: nVNS, non-invasive vagus nerve stimulation; SD, standard deviation; SoC, standard of care.

Table B24: Outcomes from the Nesbitt et al (2015) study

Study name		Nesbitt et al (2015)
Size of study groups	**Treatment**	n=19 (nVNS given as an adjunct or first-line treatment; eCH, n=8; cCH, n=11)
	Control	n=19 (SoC alone; within-patient changes from baseline; eCH, n=8; cCH, n=11)
Study duration	**Time unit**	12 months 5 cCH patients were further evaluated in a 1-year extended follow-up
Type of analysis	**ITT/per-protocol**	N/A
Prevention outcome	**Name**	Mean overall change in condition
	Unit	Patients' percentage estimates of perceived overall change in condition from baseline
Effect size	**Value**	48%[a] 1-year follow-up cCH patients (n=5): 26 weeks, 62%; 52 weeks, 58%
	Standard error mean	±9% 1-year follow-up cCH patients (n=5): 26 weeks, ±8%; 52 weeks, ±6%
Statistical test	**Type**	Paired *t* test
	***P*-value**	*P*=0.577 (26 weeks vs 52 weeks for the 1-year follow-up cCH patients)
Prevention outcome	**Name**	Mean 24-hour attack frequency
	Unit	Reduction in attacks from baseline to 12 months
Effect size	**Value**	Reduction from 4.5 to 2.6 attacks
	$F_{1,17}$	25.3
Statistical test	**Type**	General linear model with repeated measures
	***P*-value**	*P*<0.0005
Acute medication outcome	**Name**	Acute medication use
	Unit	Percentage change in other acute medication use
Effect size	**Value**	3 patients discontinued all acute use of oxygen or triptans. 10 of 14 patients reduced oxygen by a mean of 55%±8%. 9 of 12 patients reduced triptans by a mean of 48%±6%.
	Standard error mean	See above
Statistical test	**Type**	N/A
	***P*-value**	N/A
Acute outcome	**Name**	Pain-free response
	Unit	Percentage of attacks treated acutely
Effect size	**Value**	47% of all treated attacks aborted Time to pain freedom of 11 minutes (mean)
	Standard error mean	N/A
Statistical test	**Type**	N/A
	***P*-value**	N/A

Comments: [a] 79% (15/19) of patients perceived improvement in their condition.
Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; eCH, episodic cluster headache; ITT, intent-to-treat; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B25: Outcomes from the Trimboli et al (2018) study

Study name		Trimboli et al (2018)
Size of study groups	**Treatment**	n=12 (nVNS; cCH)
	Control	n=12 (within-patient control; baseline/pre-nVNS; cCH)
Study duration	**Time unit**	>4 months (>1 month baseline; 3 month nVNS)
Type of analysis	**ITT/per-protocol**	N/A
Outcome	**Name**	Responders
	Unit	Proportion of patients with a ≥30% reduction from baseline in headache days after 3 months of nVNS treatment
Effect size	**Value**	1 of 12 patients was a responder at 3 months. A slight improvement in weekly headache frequency was observed in 2 patients. 3 patients did not demonstrate any headache change. A worsening in the number of CHs per week was observed in 6 patients after 3 months of nVNS treatment.
	95% CI	N/A
Statistical test	**Type**	N/A
	***P*-value**	N/A
Other outcome	**Name**	Abortive effect
	Unit	Patients reporting relief of a CH episode
Effect size	**Value**	0 patients reported relief using nVNS.
	95% CI	N/A
Statistical test	**Type**	N/A
	***P*-value**	N/A

Comments: Abbreviations: cCH, chronic cluster headache; CH, cluster headache; CI, confidence interval; ITT, intent-to-treat; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

7.6.2 Justification of the inclusion of outcomes above from any analyses other than intention-to-treat

Intent-to-treat analyses were not included or applicable for the Marin et al (2018), Nesbitt et al (2015), and Trimboli et al (2018) studies because these studies were audits of real-world clinical experience.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Studies on adverse events (sections 7.1 to 7.6 repeated)

Identification of safety studies

Published and unpublished studies of non-invasive vagus nerve stimulation (nVNS) for cluster headache identified and appraised in sections 7.1 to 7.6 that also comprehensively reported adverse events are listed in Table B33. Details on the identification and selection of these studies and on their methodologies, critical appraisal, and efficacy results are presented in sections 7.1 to 7.6. Additional safety-specific results are presented in this section.

Published safety studies

The Medline, Embase, Medline In-Process, and Cochrane Library databases were searched for all clinical studies that included comprehensive safety evaluations of nVNS in patients with headache conditions or safety studies of nVNS focused on cardiovascular effects, a serious adverse event (AE)-related concern associated with other comparators (e.g. subcutaneous sumatriptan, invasive vagus nerve stimulation). Full details on the search strategy are provided in section 10, appendix 2.

Unpublished safety studies

On 7 March 2019, the ClinicalTrials.gov and WHO-ICTRP databases were searched for all clinical studies that included comprehensive safety evaluations of nVNS in patients with headache conditions or safety studies of

nVNS focused on cardiovascular effects. The applicable cardiovascular study identified in the electroCore Clinical Library (see section 10.2.5) was added to the unpublished study search results and is included with this submission. In the ClinicalTrials.gov search, “vagus nerve stimulation” OR “gammaCore” was specified for the intervention/treatment, and “headache” OR “migraine” OR “cardiovascular” was specified for the Other terms field. A search limit was defined to exclude studies with a status of “not yet recruiting,” “recruiting,” or “enrolling by invitation,” as results would be unavailable for such studies. In the WHO-ICTRP, search terms were “headache” OR “migraine” OR “cardiovascular” in the Title field AND “vagus nerve stimulation” OR “gammaCore” in the Intervention field. No other search limits were defined.

Search results from each database were cross-referenced, and duplicates were removed to create a master list of unique records for screening. For studies represented by more than 1 record, only the record with the most recent date was selected for inclusion. Search results that clearly did not represent safety studies of nVNS use in headache conditions or safety studies of nVNS focused on cardiovascular effects on the basis of the study title were excluded, as was the 1 unpublished study of nVNS for cluster headache previously identified and appraised in sections 7.1 to 7.6 (to avoid duplication). The NCT numbers of the remaining records were then cross-referenced with those indicated in the final full-text articles from the 2 published study searches, and duplicate studies were removed from the unpublished study search results.

The eligibility of full-text sources in the remaining search results was then assessed. Records included were required to evaluate nVNS safety in patients with headache or the cardiovascular safety of nVNS. Studies of vagus nerve stimulation devices other than the nVNS device were excluded, as were studies with no results available and studies that did not comprehensively report adverse events.

Sources determined to be eligible for qualitative synthesis were reviewed, and each item detailed in this template was extracted and entered directly into the

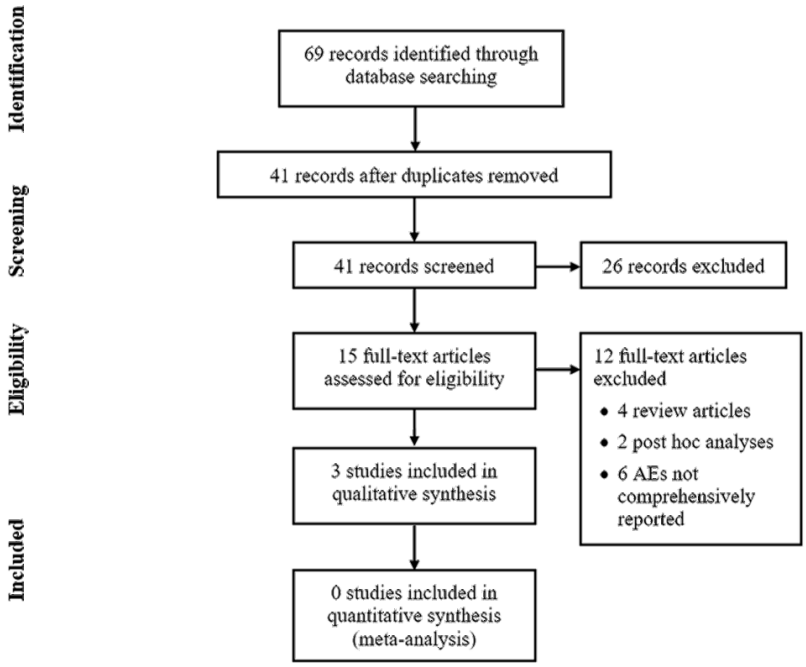
document. Data abstraction was verified by a second reviewer for accuracy and completeness.

Safety study selection

Table B26: Selection criteria used for published safety studies

Inclusion criteria	
Population	Headache, non-headache with a focus on cardiovascular adverse outcomes
Interventions	nVNS
Outcomes	Safety and tolerability/adverse events
Study design	Clinical trials
Language restrictions	English
Search dates	1 January 2005 through 6 March 2019
Exclusion criteria	
Population	Non-headache disease states (unless the study focused on cardiovascular outcomes), healthy subjects
Interventions	Treatments other than nVNS
Outcomes	Non-quantitative safety outcomes only
Study design	Post hoc analyses, reviews, studies that did not comprehensively report adverse events
Language restrictions	Non-English
Search dates	Prior to 1 January 2005

Figure B13: PRISMA diagram for published safety studies of nVNS

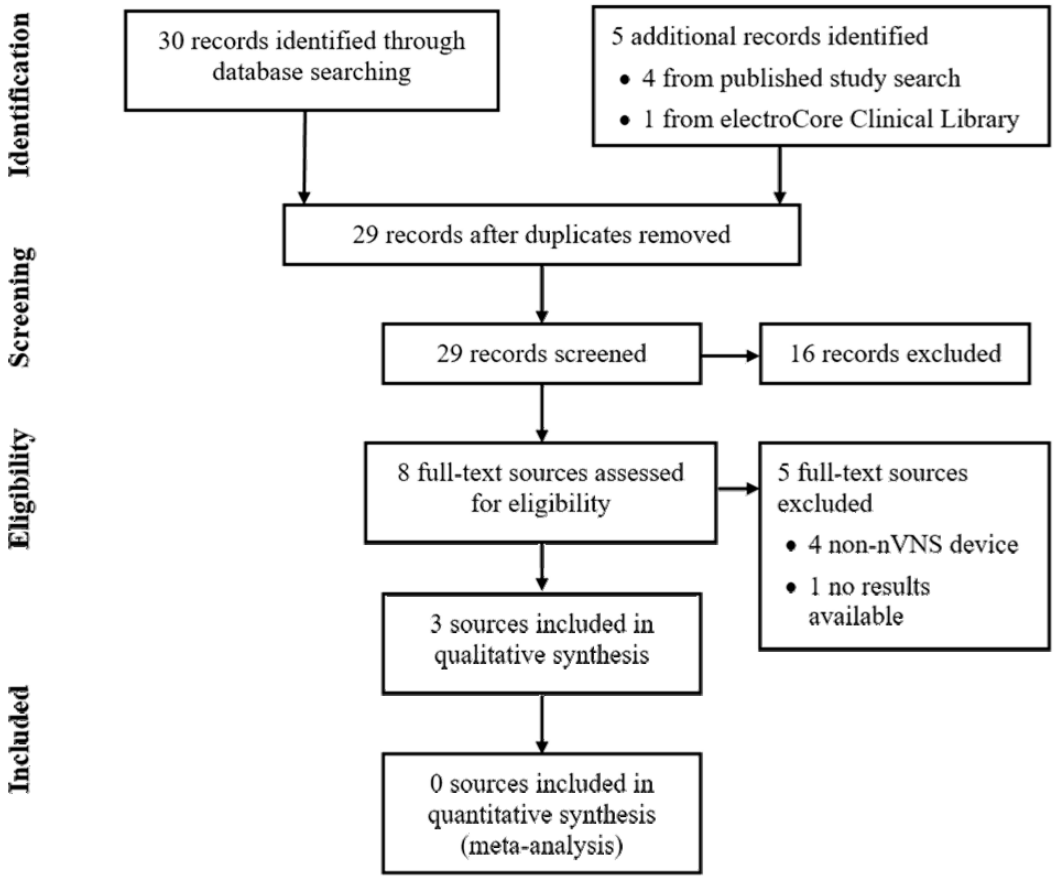


Abbreviations: AE, adverse event; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table B27: Selection criteria used for unpublished safety studies

Inclusion criteria	
Population	Headache, non-headache with a focus on cardiovascular adverse outcomes
Interventions	nVNS
Outcomes	Safety and tolerability/adverse events
Study design	Clinical trials
Language restrictions	No restrictions
Search dates	All dates
Exclusion criteria	
Population	Non-headache disease states (unless the study focused on cardiovascular outcomes), healthy subjects
Interventions	Treatments other than nVNS
Outcomes	Non-quantitative safety outcomes only
Study design	Post hoc analyses, reviews, studies that did not comprehensively report adverse events
Language restrictions	No exclusions
Search dates	No exclusions

Figure B14: PRISMA diagram for unpublished safety studies of nVNS



Abbreviations: AE, adverse event; nVNS, non-invasive vagus nerve stimulation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Complete list of relevant safety studies

All previously identified cluster headache studies that also comprehensively reported adverse events and published and unpublished safety studies selected in the systematic searches are presented in Table B33, Table B34, and Table B35 (Silberstein et al. 2016b, Goadsby et al. 2018, de Coo et al. 2017, Gaul et al. 2016, Tassorelli et al. 2018, Diener et al. 2018, Silberstein et al. 2016a, Goadsby et al. 2014, Rubenstein Engel et al. 2015, NIH - clincalTrials.gov. 2018). Copies of all published studies, a structured abstract for the future publication of the unpublished PREMIUM study (along with the most recent corresponding conference abstract and poster presentation), and copies of the conference poster presentation and study record without corresponding publications are included with this submission.

Table B33: List of previously identified and appraised cluster headache studies comprehensively reporting safety

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Silberstein SD, Mechtler LL, Kudrow DB, et al. *Headache*. 2016;56(8):1317-1332.	ACT1	Episodic and chronic cluster headache (US)	nVNS (acute)	Sham
Goadsby PJ, de Coo IF, Silver N, et al. *Cephalalgia*. 2018;38(5):959-969.	ACT2	Episodic and chronic cluster headache (EU)	nVNS (acute)	Sham
de Coo IF, Marin JCA, Silberstein SD, et al. 30 January 2019.	de Coo et al (2019)	Episodic and chronic cluster headache (pooled analysis of ACT1 and ACT2)	nVNS (acute)	Sham
Gaul C, Diener H-C, Silver N, et al. *Cephalalgia*. 2016;36(6):534-546.	PREVA	Chronic cluster headache (EU)	SoC+nVNS (preventive)	SoC alone

Abbreviations: nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B34: List of relevant published safety studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Tassorelli C, Grazzi L, de Tommaso M, et al. *Neurology*. 2018;91(4):e364-e373.	PRESTO	Episodic migraine (EU)	nVNS (acute)	Sham
Silberstein SD, Calhoun AH, Lipton RB, et al. *Neurology*. 2016;87(5):529-538.	EVENT	Chronic migraine (US)	nVNS (preventive)	Sham
Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. *Cephalalgia*. 2014;34(12):986-993.	Goadsby et al (2014)	Migraine (US)	nVNS (acute)	N/A

Abbreviation: nVNS, non-invasive vagus nerve stimulation.

Table B35: List of relevant unpublished safety studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Diener H-C, Goadsby PJ, Ashina M, et al. 8 January 2019.	PREMIUM	Episodic migraine (EU)	nVNS (preventive)	Sham
Rubenstein Engel E, Blake J, Liebler E. Presented at: 67th AAN Meeting; April 18-25, 2015; Washington, DC.	Rubenstein Engel et al (2015)	Asthma (assessment of cardiovascular AEs) (US)	nVNS	N/A
NIH. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03410628. Accessed: 7 March 2019.	NCT03410628	Migraine (pain and allodynia symptoms) (South Africa)	nVNS (acute)	N/A

Abbreviations: AAN, American Academy of Neurology; AE, adverse event; NIH, National Institutes of Health; nVNS, non-invasive vagus nerve stimulation.

Summary of methodology of safety studies

Table B36: Summary of methodology for the PRESTO study

Study name	**PRESTO**
Objectives	To compare clinically meaningful outcomes of acute nVNS treatment with those of a sham device in participants with episodic migraine and to evaluate the safety and tolerability of nVNS
Location	10 Italian sites
Design	Randomised, double-blind, parallel-group, sham-controlled, prospective study
Duration of study	12 weeks
Sample size	A sample size of 232 participants (116 per treatment arm) was determined to provide 90% power to demonstrate statistical significance for the primary endpoint, assuming a sham pain-free rate of 18%, a treatment difference of 20%, an α value of 0.05, and an attrition rate of 10%.
Inclusion criteria	Adults with a previous diagnosis of migraine with or without aura according to ICHD-3 beta criteria who were <50 years of age at migraine onset and had 3 to 8 attacks per month with <15 headache days per month during the last 6 months
Exclusion criteria	History of secondary headache, aneurysm, intracranial haemorrhage, brain tumours, significant head trauma, substance abuse, addiction, syncope, or seizure; another significant pain disorder; cardiovascular/cerebrovascular disease; uncontrolled hypertension; psychiatric/cognitive disorders; pregnancy; medical condition requiring oral/injectable steroids; botulinum toxin injections in the past 6 months; head or neck nerve blocks in the past 2 months; previous migraine prevention surgery, cervical vagotomy, electrical device, or metal cervical spine hardware implantation; current use of opioids for more than 2 days per month; current use of simple analgesics or nonsteroidal anti-inflammatory drugs for more than 15 days per month; current use of triptans, ergots, or combined analgesics for more than 10 days per month; and initiation of preventive migraine medications in the past 2 months
Method of randomisation	Participants were randomly assigned (1:1 ratio) to receive nVNS or sham (variable block design [4 and 6], stratified by site) according to independent statistician-generated randomisation schedules.
Method of blinding	A third-party distributor allocated the devices to the sites. Devices were labelled with serial numbers and not outwardly identified as active or sham. The Merge eClinical OS Interactive Web Response System provided study site personnel (investigator or designee) with a sequential participant randomisation number and corresponding device serial number. A sponsor designee provided the randomisation schedule to a site-identified unblinded trainer. The trainer was unblinded to provide participants with instructions that were specific to the assigned device and had no further interaction with participants.

Study name	**PRESTO**
Intervention(s) (n=) and comparator(s) (n=)	Acute treatment of migraine with bilateral 120-second stimulations using nVNS (n=122) or a sham device (n=126) administered within 20 minutes of migraine pain onset and repeated if the pain had not improved after 15 minutes (with an optional additional set of bilateral stimulations for participants who were not pain free after 120 minutes)
Baseline differences	Demographic and baseline characteristics were generally well balanced between the nVNS and sham groups.
Duration of follow-up, lost to follow-up information	4 weeks (run-in period); 4 weeks (double-blind period); 4 weeks (open-label period); 4 patients were lost to follow-up
Statistical tests	A logistic regression analysis was included in the primary endpoint (pain freedom at 120 minutes for the first attack in the double-blind period) with adjustment for the participants' baseline pain score, use of preventive therapies, and presence of aura and was repeated for the 30- and 60-minute time points; the presence of aura was not considered in the 30-minute analysis because of model fit issues. A post hoc repeated-measures analysis using generalised linear mixed-effects regression models was conducted to gain further insight from all of the data collected at multiple time points through the 120-minute time point of the primary efficacy analysis. The repeated-measures analysis was also adjusted for baseline pain score, use of preventive therapies, and presence of aura. Mean percentage changes in pain score were compared between treatment groups using 2-sample *t* tests. The remaining secondary and other analyses were evaluated using the χ^2 test or Fisher exact test, as appropriate. Two-sided *P* values <0.05 were considered statistically significant. Use of rescue medication before the 120-minute assessment was considered a study treatment failure.
Primary outcomes (including scoring methods and timing of assessments)	The proportion of participants who were pain free without using rescue medication at 120 minutes after study treatment completion for the first treated migraine attack of the double-blind period
Secondary outcomes (including scoring methods and timing of assessments)	Efficacy: Key secondary and other efficacy endpoints for the first treated attack during the double-blind period included pain-free rates at 30 and 60 minutes; pain relief at 30, 60, and 120 minutes; mean percentage change in pain score from baseline to 30, 60, and 120 minutes; and the absence of associated symptoms (i.e. nausea, vomiting, photophobia, and phonophobia) at 120 minutes. *Pain relief* was defined according to the IHS guidelines for controlled studies of migraine medications as a decrease in pain intensity from moderate (2) or severe (3) to mild (1) or no (0) pain on a 4-point scale. Consistency of response was evaluated during the double-blind period by calculating ≥50% responder rates at 120 minutes for both pain freedom and relief in those with at least 2 treated migraine attacks. Pain freedom and pain relief were also evaluated at 120 minutes after the first treated attack in the open-label period, as was the consistency of response for those who treated at least 2 attacks during this period. Safety and tolerability: These were assessed by comparing rates of AEs, adverse device effects, and SAEs among the nVNS group and controls. Other: Additional outcomes included blinding effectiveness, participant satisfaction (1, extremely satisfied; 5, not at all satisfied), participant willingness to recommend the device to a friend or family member, and ease of device use (1, very easy; 4, very difficult).

Abbreviations: AE, adverse event; ICHD, International Classification of Headache Disorders; IHS, International Headache Society; nVNS, non-invasive vagus nerve stimulation; SAE, serious adverse event.

Table B37: Summary of methodology for the PREMIUM study

Study name	**PREMIUM**
Objectives	To evaluate the efficacy, tolerability, and safety of nVNS for the preventive treatment of episodic migraine
Location	22 European sites
Design	Randomised, double-blind, sham-controlled, parallel-group, prospective study
Duration of study	36 weeks

Study name	**PREMIUM**
Sample size	A sample size of 320 patients (160 per treatment arm) was determined to provide 90% power to demonstrate statistical significance for the primary outcome, assuming a treatment difference of 1 migraine day, a common standard deviation of 2.5, a type I error of 5%, and an attrition rate of 15% in the double-blind period.
Inclusion criteria	Adults with a previous diagnosis of migraine with or without aura according to ICHD-3 beta criteria who were <50 years of age at migraine onset and had 5 to 12 migraine days per month, with at least 2 migraines lasting >4 hours
Exclusion criteria	Chronic migraine diagnosis; previous diagnosis of medication overuse headache that reverted to episodic migraine in the past 6 months; medical condition requiring oral/injectable steroids; history of secondary headache, aneurysm, intracranial haemorrhage, brain tumours, significant head trauma, substance abuse, addiction, syncope, or seizure; structural abnormality, pain, or metal cervical spine hardware implantation near the treatment site; another significant pain disorder; cardiovascular/cerebrovascular disease; abnormal electrocardiogram; previous migraine prevention surgery, cervical vagotomy, or electrical or neurostimulator device implantation; uncontrolled hypertension; psychiatric/cognitive disorders; pregnancy; botulinum toxin injections in the past 6 months; head or neck nerve blocks in the past 2 months; failure of at least 3 classes of migraine prevention drugs; opioid use (more than 2 days per month); marijuana use (more than twice per month); simple analgesic or nonsteroidal anti-inflammatory drug use (more than 15 days per month); triptan, ergot, or combined analgesic use (more than 10 days per month)
Method of randomisation	Patients were randomly assigned to receive nVNS or a sham control device (allocation, 1:1) under variable block sizes of 4 and 6, where 4 was chosen approximately 60% of the time and 6 was chosen approximately 40% of the time. Randomisation was stratified by study site, according to independent third-party–generated randomisation schedules. The investigator or his or her designee at each site entered the required study and patient information into the Merge eClinical OS Interactive Web Response System used for randomisation and obtained a sequential patient randomisation number and corresponding device serial number.
Method of blinding	A third-party distributor issued the devices to the study sites. A sponsor designee provided a copy of the randomisation schemes to the unblinded trainer at each study centre. The unblinded trainer opened the box, used the study device to train the subject, and provided the device to the patient after training.
Intervention(s) (n=) and comparator(s) (n=)	Preventive treatment with nVNS (n=169) or sham (n=172), consisting of 2 consecutive bilateral stimulations administered 3 times per day (upon waking and 6 to 8 hours after the first and second daily treatments)
Baseline differences	Demographics and baseline characteristics were well balanced between the nVNS and sham groups.
Duration of follow-up, lost to follow-up information	12 weeks (double-blind period); 24 weeks (open-label period); 15 patents lost to follow-up
Statistical tests	For continuous and categorical variables, *P* values were derived from linear regression (ANCOVA models) and logistic regression, respectively, adjusted for treatment group, centre, presence/absence of aura, and number of migraine/headache/acute medication days in the run-in period. Two-sided *P* values <0.05 were considered statistically significant.
Primary outcomes (including scoring methods and timing of assessments)	The primary efficacy outcome was the mean reduction in the number of migraine days from the 4-week run-in period (baseline) to the last 4 weeks of the 12-week double-blind period. *Migraine day* was defined as a migraine headache occurring in a 24-hour period.

Study name	**PREMIUM**
Secondary outcomes (including scoring methods and timing of assessments)	Efficacy: The mean reduction in the number of headache days and acute medication days from the 4-week run-in period (baseline) to the last 4 weeks of the 12-week double-blind period were evaluated as secondary outcomes. A *headache day* was defined as any headache occurring in a single calendar day. Other secondary outcomes included ≥50% responder rates for migraine, headache, and acute medication days (with a *responder* defined as a patient who recorded a reduction of ≥50% from baseline to the last 4 weeks of the double-blind period) and migraine and headache day reductions during the open-label period. Safety and tolerability: These were assessed using rates of AEs, adverse device effects (including those considered serious), and study discontinuations due to AEs. Other: Blinding effectiveness was evaluated in the double-blind period at 1 week and at completion by asking patients to indicate which treatment they thought they had received (active stimulation, sham, or don't know). Device perceptions were determined from patient responses for satisfaction (1, extremely satisfied; 5, not at all satisfied) and ease of use (1, very easy; 4, very difficult).

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; ICHD, International Classification of Headache Disorders; nVNS, non-invasive vagus nerve stimulation.

Table B38: Summary of methodology for the EVENT study

Study name	**EVENT**
Objectives	To evaluate the feasibility, safety, and tolerability of nVNS for the prevention of CM attacks
Location	6 US sites
Design	Prospective, multicentre, randomised, double-blind, sham-controlled pilot study
Duration of study	9 months: baseline phase (1 month); randomised phase (2 months); open-label phase (6 months)
Sample size	No formal sample size calculations were performed; the sample size was selected to facilitate initial assessment of feasibility and tolerability in a clinically relevant number of participants.
Inclusion criteria	Participants were aged 18-65 years and were previously diagnosed with CM with/without aura according to the revised ICHD, 2nd edition criteria, had migraine onset before 50 years of age, and had ≥15 headache days/month during the previous 3 months.
Exclusion criteria	History of aneurysm, intracranial haemorrhage, brain tumour, or head trauma; a lesion, dysaesthesia, previous surgery, or abnormal anatomy at the treatment site; known or suspected cardiovascular disease; uncontrolled hypertension; abnormal ECG results; recent myocardial infarction; an implanted electrical/neurostimulator device; metallic implant/metal cervical spine hardware near the stimulation site; previous surgery for migraine prevention; onabotulinumtoxinA injections for migraine prevention during the previous 6 months; and prophylactic migraine medication during the previous 30 days. Modifications in prophylactic medication type/dose for indications other than CM that could interfere with the study were not permitted.
Method of randomisation	An independent statistician generated a randomisation schedule to assign participants 1:1 (variable block design stratified by study centre) to nVNS or sham treatment.
Method of blinding	Participants, investigators, and study coordinators were blinded to treatment assignment during the randomised phase. The study sponsor pre-labelled the devices according to each site's randomisation scheme; a third-party distributor provided the devices to the study sites.
Intervention(s) (n=) and comparator(s) (n=)	Preventive treatment with nVNS (n=30) or sham (n=29), consisting of 2 stimulations (5-10 minutes apart) administered to the right side of the neck 3 times per day (within 1 hour of waking, 6-8 hours after the first treatment, and 6-8 hours after the second treatment)
Baseline differences	Demographic and baseline characteristics were similar among nVNS and sham treatment groups and similar to those reported in other migraine studies
Duration of follow-up, lost to follow-up information	Following the 2-month randomised phase, the open-label phase was 6 months. 2 patients were lost to follow-up.

Study name	**EVENT**
Statistical tests	All analyses were conducted on the ITT population, which included all participants who were randomly assigned to treatment and provided data for each outcome. Missing data were imputed using last observation carried forward (LOCF). To assess the effect of protocol deviation and discontinuations, sensitivity analyses were performed on the PP population, which included only participants who completed each phase with no major protocol violations. Pooled participants from both treatment groups in the PP population (i.e. the PP completer population) were stratified and analysed by the total duration of nVNS treatment completed throughout the study (2-, 4-, 6-, or 8-month completers). Specifically, 2-month completers comprised participants in the nVNS group who completed the 2-month randomised phase and participants in the sham group (controls) who completed 2 months of open-label nVNS treatment. There were no formal a priori statistical analyses; exploratory post hoc analyses were conducted to determine the effect of nVNS treatment duration on the mean change in number of headache days and to compare treatment responses for nVNS and sham. Categorical variables were compared using the Fisher exact test (if ≥1 cell had an expected frequency ≤5) or χ^2 analyses. Continuous variables were compared using the Student *t* test and the Wilcoxon rank sum test for normal and non-normal distributions, respectively. Blinding questionnaire results were analysed using the Bang index and corresponding 95% CIs.
Primary outcomes (including scoring methods and timing of assessments)	Safety and tolerability as reported in participants' diaries during the randomised and open-label phases. Investigators categorised the onset, type, severity (mild, moderate, severe), and frequency of AEs according to treatment relatedness. Serious AEs were defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Good Clinical Practice.
Secondary outcomes (including scoring methods and timing of assessments)	Efficacy and satisfaction data. The number of reported headache days per month was normalised to the number of headache days per 28 days, which was the primary efficacy measure. A *headache day* was defined as any day on which a participant recorded a headache. The mean change from baseline in the number of headache days was evaluated at the end of the randomised phase (month 2) and through the end of the open-label phase (at 4, 6, and 8 months of treatment). Post hoc efficacy analyses assessed the effect of treatment duration on the number of headache days and determined the *percent treatment response*, defined as the proportion of participants who demonstrated ≥50% reduction from baseline in the number of headache days. The rate of patient-reported acute medication use and treatment adherence, satisfaction, and ease of use were evaluated throughout both phases. Treatment adherence ([actual number of administered treatments]/[total number of scheduled treatments] x 100) was calculated as the average daily adherence. Treatment satisfaction was assessed on a 5-point scale (extremely satisfied to not at all satisfied). Ease of use was rated on a 4-point scale (very easy to very difficult). One week into the randomised phase and at its end, study blinding effectiveness questionnaires were completed.

Abbreviations: AE, adverse event; CM, chronic migraine; CI, confidence interval; ECG; electrocardiogram; ICHD, International Classification of Headache Disorders; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation; PP, per-protocol.

Table B39: Summary of methodology for the Goadsby et al (2014) study

Study name	**Goadsby et al (2014)**
Objectives	To assess a novel, non-invasive, portable nVNS device for acute treatment of migraine
Location	4 US headache centres
Design	Open-label, single-arm, multiple-attack study
Duration of study	6 weeks (or 4 treated attacks)
Patient population	30 enrolled; 27 in the full analysis set
Sample size	No sample size calculation reported; sample size was in line with a pilot study for a device in migraine

Study name	**Goadsby et al (2014)**
Inclusion criteria	A) Between the ages of 18 and 55 years. B) Previously diagnosed with migraine with and without aura by the criteria of the ICHD-II. C) Experiences at least 2 migraines per month and less than 15 headache days per month over the previous 3 months. D) Age at onset of migraine less than 50 years old. E) Able to distinguish migraine from other headaches (e.g. tension-type headache). F) Agrees to withhold usual migraine medications until 2 hours after stimulation treatment with the nVNS device. G) Capable of completing headache pain self-assessments. H) Agrees to use the nVNS device as intended and follow all of the requirements of the study, including follow-up visit requirements. I) Agrees to report use of the nVNS device, study data, and any adverse device effects to the study centre within 24 hours of treatment(s) and agrees to schedule an office visit 7±3 days after the third and final at-home treatment or when 6 weeks has passed, whichever comes first. J) Is able to give written informed consent.
Exclusion criteria	A) Has a history of aneurysm, intracerebral haemorrhage, brain tumours, or significant head trauma. B) Has a lesion, including lymphadenopathy, at the nVNS treatment site. C) Has known or suspected severe atherosclerotic cardiovascular disease, severe carotid artery disease (e.g. bruits or history of TIA, CVA, or CHF). D) Has a history or baseline electrocardiogram (ECG) that identifies the presence of a clinically significant unstable cardiac arrhythmia, second-degree heart block type II, history of ventricular tachycardia or ventricular fibrillation, or known cardiac syndromes that may be associated with increased risk of sudden death in otherwise healthy people. E) Had a previous bilateral or right cervical vagotomy. F) Has a clinically significant irregular heart rate or rhythm. G) Has uncontrolled high blood pressure. H) Is currently implanted with an electrical and/or neurostimulator device, including but not limited to cardiac pacemaker, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant. I) Has a history of carotid endarterectomy or vascular neck surgery on the right side. J) Has been implanted with metal cervical spine hardware. K) Has a recent or repeated history of syncope. L) Has a recent or repeated history of seizure. M) Has a history or suspicion of substance abuse. N) Takes medication for acute headaches more than 10 days per month. O) Has had a change in medications for migraine prophylaxis in the previous 30 days. P) Has previously failed to respond to more than two classes of treatment for episodic migraine. Q) In the opinion of the investigator/research staff the subject is incapable of operating the nVNS device as intended and performing the data collection procedures. R) Is pregnant or is thinking of becoming pregnant in the next three months. S) Is participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days. T) Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled, prisoner). U) Is a relative of or an employee of the investigator or the clinical study site.
Intervention(s) (n=) and comparator(s) (n=)	Acute treatment with nVNS (n=27), consisting of 2 stimulations administered to the right side of the neck
Baseline differences	N/A; no comparator group at baseline
How were participants followed up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Office visit scheduled 7±3 days after the third and final at-home treatment or when 6 weeks had passed, whichever came first
Statistical tests	Summary measures as appropriate to the scale of measurement
Primary outcomes (including scoring methods and timing of assessments)	Device safety. Data on tolerability and safety were collected with a subject diary to assess onset, type, severity, and frequency of any anticipated or unanticipated adverse events, including a determination of device-relatedness.

Study name	**Goadsby et al (2014)**
Secondary outcomes (including scoring methods and timing of assessments)	Effectiveness data included headache pain on a scale of none, mild, moderate, or severe; nausea on a scale of none, mild, moderate, or severe; presence of photophobia or phonophobia; functional disability on a 4-point scale; ease of use of the device on a 4-point scale; subject satisfaction; and duration of treatment effect out to 24 hours by measuring use of rescue medication in the 24 hours after treatment and time to meaningful relief.

Abbreviations: CHF, congestive heart failure; CVA, cerebral vascular attack; ICHD, International Classification of Headache Disorders; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; TIA, transient ischemic attack.

Table B40: Summary of methodology for the Rubenstein Engel et al (2015) study

Study name	**Rubenstein Engel et al (2015)**
Objectives	This report describes the cardiovascular safety of the nVNS device when used to treat acute bronchospasm in patients with asthma. (The primary objective of the phase 2 study was to obtain preliminary data regarding the safety and clinical benefits of nVNS for the relief of acute bronchoconstriction in subjects with asthma.)
Location	4 investigational sites in the United States
Design	Open-label, phase 2, multicentre, prospective, single-arm, interventional pilot study
Duration of study	3 study visits: baseline; nVNS; 7 days
Patient population	30 patients with asthma; 29 with cardiac assessments
Sample size	No sample size calculation reported
Inclusion criteria	Men or women aged 18 to 65 years with a history of mild to moderate asthma exacerbations for at least 1 year prior to enrolment; use of an inhaled short-acting β-agonist (e.g. albuterol) to reverse asthma symptoms; reversibility of forced expiratory volume in the first second of expiration of ≥12% within 15 to 30 minutes after 4 inhalations of albuterol
Exclusion criteria	None provided
Intervention(s) (n=) and comparator(s) (n=)	nVNS (n=30) (a total of 284 ECGs were performed for 29 of 30 patients); no comparator group
Baseline differences	N/A; no comparator group at baseline
How were participants followed up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Follow-up at 7 days after treatment; one subject was excluded from ECG findings because only 1 ECG reading was taken during the treatment visit
Statistical tests	Descriptive statistics (i.e. mean values ± SEM) were used to assess ECG parameters.
Primary outcomes (including scoring methods and timing of assessments)	Safety (inferred from objectives): 1) assessment of cardiac function with 12-lead ECG at baseline (timing not specified), treatment visit (pre-, during, post-nVNS), and follow-up (7 days post-nVNS); the ECG parameters measured were heart rate, PR interval, QTc interval, and QRS duration; 2) cardiac rhythms (i.e. PACs, PVCs, arrhythmias, SAs).

Study name	**Rubenstein Engel et al (2015)**
Secondary outcomes (including scoring methods and timing of assessments)	Clinical benefit (inferred from objectives): no specific outcomes provided

Abbreviations: AE, adverse event; ECG; electrocardiogram; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; PAC, premature atrial contraction; PVC, premature ventricular contraction; QTc, corrected QT; SA, sinus arrhythmia; SEM, standard error of the mean.

Table B41: Summary of methodology for the NCT03410628 study

Study name	**NCT03410628 (Terminated)[a]**
Objectives	To gather preliminary information on the safety and effectiveness of patient self-administration of non-invasive neurostimulation of the vagus nerve using the nVNS device for the treatment of pain and allodynia symptoms associated with acute migraine in adults
Location	5 South African study centres
Design	Prospective, open-label, multicentre feasibility study
Duration of study	Each subject enrolled in this study will treat up to 3 migraine headaches at home over a period of up to 6 weeks
Patient population	21 patients with migraine
Sample size	N/A; not provided
Inclusion criteria	A) Is between the ages of 18 and 55 years. B) Has been previously diagnosed as suffering from migraine, in accordance with the IHS Classification criteria (2nd) (with or without aura). C) Has experienced at least 2 migraines per month, but less than 15 headache days per month (over the last 3 months). D) Has age at onset of migraine less than 50 years. E) Is able to distinguish migraines from other headaches (e.g. tension headaches). F) Agrees to withhold usual migraine medications until after stimulation treatment with the nVNS device. G) Agrees to follow all of the requirements of the study, including follow-up visit requirements, and is sufficiently trained with respect to the operation of the nVNS device and the data collection procedures. H) Agrees to report use of the nVNS device, study data, and any adverse device effects to the study centre within 24 hours of treatment(s) and agrees to schedule an office visit 4-10 days after the third and final treatment or when 6 weeks has passed, whichever comes first. I) Is able to give written informed consent, or his/her legally authorised representative is available to give written informed consent.
Exclusion criteria	A) Has a history of aneurysm, bleed, brain tumours, or significant head trauma. B) Has a lesion (including lymphadenopathy) at the therapy head placement site. C) Has known or suspected severe atherosclerotic cardiovascular disease, carotid artery disease (e.g. bruits or history of TIA or CVA), or CHF. D) Has a history of epilepsy. E) Has suspected or confirmed sepsis or infection. F) Has a clinically significant irregular heart rate or rhythm. G) Is receiving pressors to maintain blood pressure. H) Has a history of syncope. I) Is currently implanted with an electrical and/or neurostimulator device, including but not limited to cardiac pacemaker, vagal neurostimulator, deep brain stimulator, spinal stimulator, bone growth stimulator, or cochlear implant. J) Has been implanted with metal cervical spine hardware. K) Has a history of carotid endarterectomy or vascular neck surgery on the right side. L) Has a condition that would interfere with headache pain self-assessment. M) Is pregnant or is thinking of becoming pregnant in the next 6 weeks. N) Is participating in any other therapeutic clinical investigation or has participated in a clinical trial in the preceding 30 days. O) Takes medication for acute headaches more than 10 days per month. P) Has a history or suspicion of substance abuse. Q) Belongs to a vulnerable population or has any condition such that his or her ability to provide informed consent, comply with follow-up requirements, or provide self-assessments is compromised (e.g. homeless, developmentally disabled, prisoner).
Intervention(s) (n=) and comparator(s) (n=)	nVNS (n=21); no comparator group

Study name	**NCT03410628 (Terminated)[a]**
Baseline differences	N/A; no comparator group at baseline
How were participants followed up (e.g. through pro-active follow-up or passively)? Duration of follow-up, participants lost to follow-up	Up to 3 migraines treated over a period of 6 weeks; follow-up of up to 4 months
Statistical tests	Descriptive statistics
Primary outcomes (including scoring methods and timing of assessments)	Safety was assessed by collecting adverse events for the duration of the study (i.e. up to 4 months.
Secondary outcomes (including scoring methods and timing of assessments)	Change in headache pain severity from baseline to 120 minutes for first treated migraine attack. Subjects completed headache pain scores using a 4-point scale (wherein 3=severe, 2=moderate, 1=mild, and 0=no pain) at baseline (0 minutes) and 120 minutes.

[a] This study was terminated based on the sponsor's decision to initiate and focus on larger-scale clinical trials in North American and Europe.
Abbreviations: AE, adverse event; CHF, congestive heart failure; CI, confidence interval; CVA, cerebral vascular attack; IHS, International Headache Society; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; TIA, transient ischemic attack.

Details on data from any single safety study summarized above that have been drawn from more than one source

Beyond the primary publication for the PRESTO study described above, additional data obtained from this study were reported in 2 separate sources (Grazzi et al. 2018, Martelletti et al. 2018). These sources, which focused on efficacy outcomes in the treatment of migraine, are not discussed further because all adverse event data relevant to this section are reflected in the primary publication.

Differences between patient populations and methodology in the above safety studies

The safety studies identified in the published and unpublished study searches that comprehensively reported adverse events comprised different populations (PRESTO, 248 episodic migraine patients; PREMIUM, 341 episodic migraine patients; EVENT, 59 chronic migraine patients; Goadsby et

al [2014], 27 migraine patients; Rubenstein Engel et al [2015], 29 asthma patients; NCT03410628, 21 migraine patients). The PRESTO and PREMIUM trials were randomised, double-blind, sham-controlled studies of patients with episodic migraine receiving acute and preventive migraine treatment, respectively. EVENT was a randomised, double-blind, sham-controlled study of migraine prevention, whereas the Goadsby et al (2014), Rubenstein Engel et al (2015), and NCT03410628 studies were observational studies of acute treatment. The Rubenstein Engel et al (2015) study was designed specifically to assess the cardiovascular safety of nVNS. The preventive stimulation protocol used in PREMIUM and EVENT was two 2-minute stimulations administered 3 times per day, with bilateral stimulations used in PREMIUM and right-side stimulations used in EVENT. The acute stimulation protocols used in the PRESTO and Goadsby et al (2014) studies each comprised 2 stimulations, with PRESTO using 2-minute bilateral stimulations and Goadsby et al using 90-second right-side stimulations. Only a single 90-second stimulation was used in the Rubenstein Engel et al (2015) study (right-side stimulation) and NCT03410628 study (side of stimulation not specified).

Details of subgroup analyses that were undertaken in the safety studies summarised above (rationale and prespecified/post hoc)

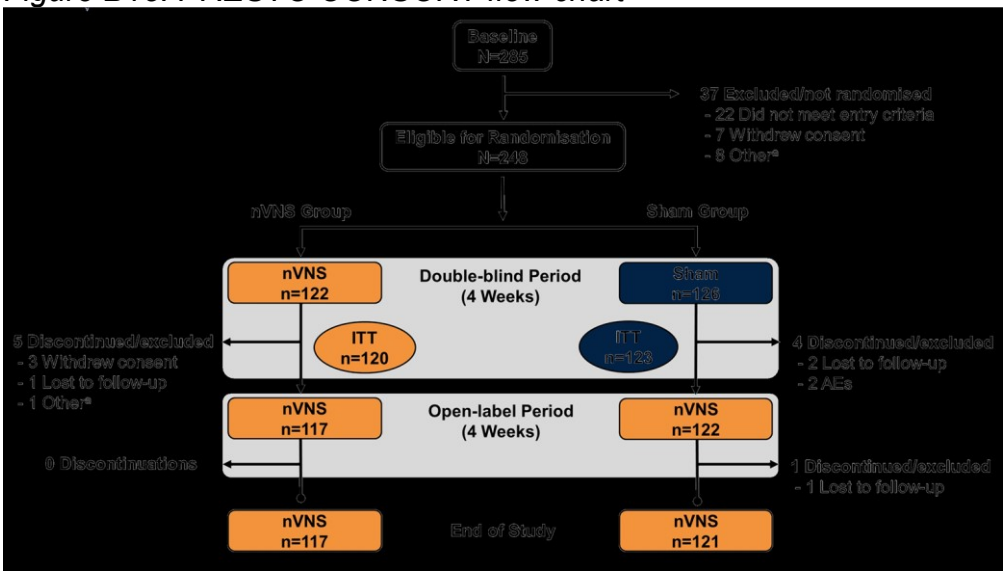
Not applicable.

Details of the numbers of patients who were enrolled, randomised, and allocated to each treatment

For the PRESTO, PREMIUM, EVENT, and Goadsby et al (2014) studies, details on patient disposition, including patients who were enrolled, randomised, and allocated to treatment, as well as reasons for study discontinuation, are provided below in the flow charts (Figure B15, Figure B16, Figure B17, Figure B18). The Rubenstein Engel et al (2015) and NCT03410628 studies were open-label, single-arm pilot/feasibility studies, with no randomisation or comparator group. The Rubenstein Engel et al (2015) study evaluated 29 of its 30 enrolled patients who received nVNS, with 1 patient excluded because he or she had only 1 ECG reading during the

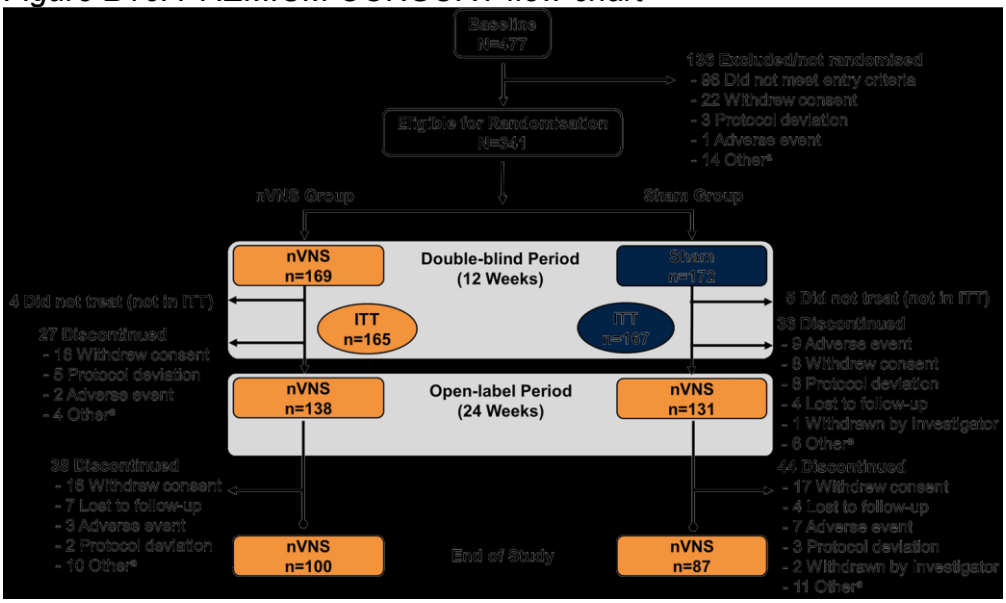
treatment visit. For NCT03410628, no patients were withdrawn from the study, but 6 of 21 patients did not complete the evaluations because the study was terminated based on the sponsor's decision to initiate and focus on larger-scale clinical trials in North American and Europe.

Figure B15: PRESTO CONSORT flow chart



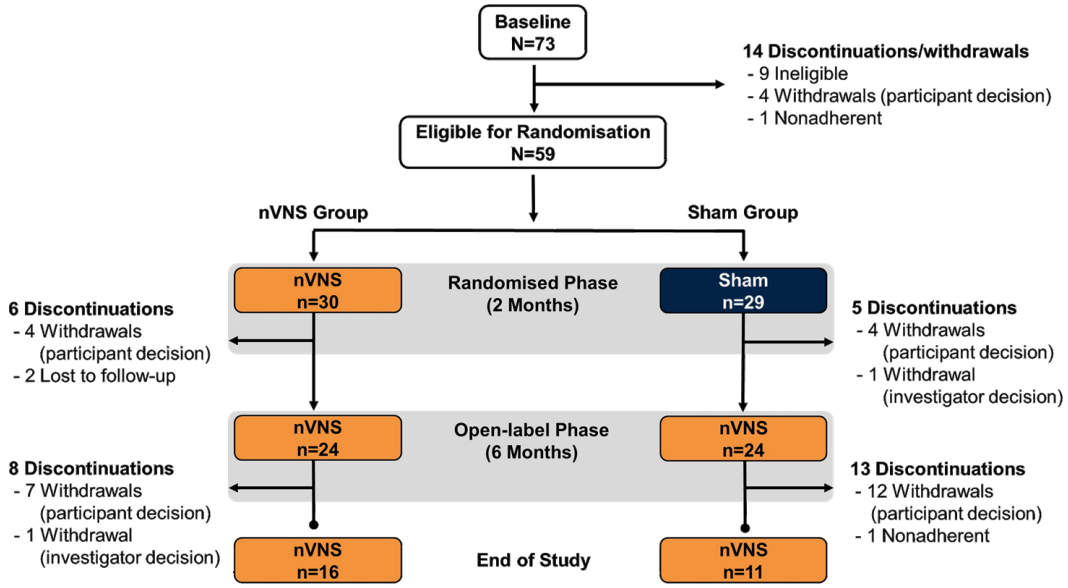
[a] Other reasons for discontinuation included inability to fulfil visits because of injury, inability to continue the study because of family commitments, dissatisfaction with or discontinued/lack of use of the device, and noncompliance with study procedures.
Abbreviations: AE, adverse event; ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Figure B16: PREMIUM CONSORT flow chart



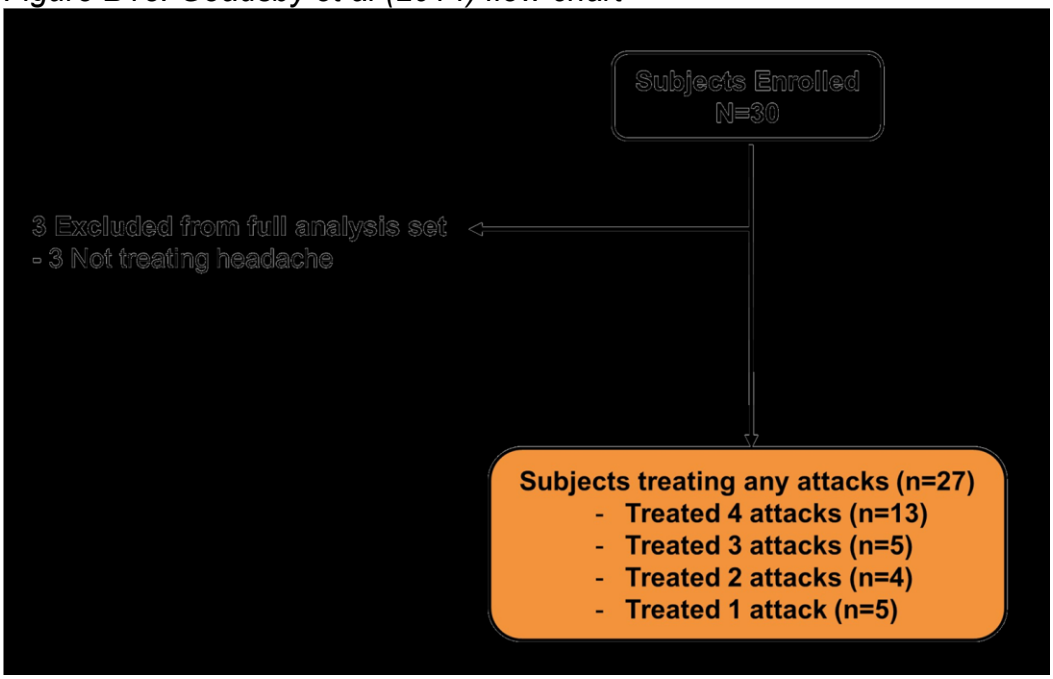
[a] Other reasons for discontinuation included inability to fulfil visits because of illness, travel, or family commitments, subject decision, and noncompliance with study procedures.
Abbreviations: ITT, intent-to-treat; nVNS, non-invasive vagus nerve stimulation.

Figure B17: EVENT CONSORT flow chart



Abbreviation: nVNS, non-invasive vagus nerve stimulation.

Figure B18: Goadsby et al (2014) flow chart



Details of and the rationale for patients who were lost to follow-up or withdrew from the studies

Details for patients who withdrew from the studies are provided above.

Critical appraisal of safety studies

Table B42: Critical appraisal of the PRESTO study

Study name	**PRESTO**	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Participants were randomly assigned (1:1 allocation) to receive nVNS or sham (variable block design [4 and 6], stratified by site) according to independent statistician-generated randomisation schedules.
Was the concealment of treatment allocation adequate?	Yes	A third-party distributor allocated the devices to the sites. Devices were labelled with serial numbers and not outwardly identified as active or sham. The Merge eClinical OS Interactive Web Response System provided study site personnel (investigator or designee) with a sequential participant randomisation number and corresponding device serial number. A sponsor designee provided the randomisation schedule to a site-identified unblinded trainer. The trainer was unblinded to provide participants with instructions that were specific to the assigned device and had no further interaction with participants.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Disease/attack characteristics at baseline were similar between the treatment groups.
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Missing pain intensity data were imputed using the last observation carried forward. Subjects who did not provide data on associated symptoms were excluded from symptom-specific analyses.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, UK: Centre for Reviews and Dissemination.
Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B43: Critical appraisal of the PREMIUM study

Study name	**PREMIUM**	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Patients were randomly assigned to receive nVNS or a sham control device (1:1 allocation) under variable block sizes of 4 and 6, where 4 was chosen approximately 60% of the time and 6 was chosen approximately 40% of the time. Randomisation was stratified by study site, according to independent third-party–generated randomisation schedules.
Was the concealment of treatment allocation adequate?	Yes	The investigator or his or her designee at each site entered the required study and patient information into the Merge eClinical OS Interactive Web Response System used for randomisation and obtained a sequential patient randomisation number and corresponding device serial number.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Disease characteristics at baseline were similar between the treatment groups.
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Available data from prematurely withdrawn subjects were included in the analysis as far as possible. When data were only partially completed for either the 4-week run-in period or the last 4 weeks in the 12-week double-blind period, available data were converted to a 4-week interval. That is, if data were collected for 2 weeks within a 4-week interval, the data were converted to a 4-week period by multiplying the data by 2. Missing data were analysed and imputed using an appropriate method.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, UK: Centre for Reviews and Dissemination.
Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B44: Critical appraisal of the EVENT study

Study name	**EVENT**	
Study question	**Response**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	An independent statistician generated a randomisation schedule to assign participants 1:1 (variable block design stratified by study centre) to prophylactic treatment with nVNS or sham treatment. The study sponsor pre-labelled the devices according to each site's randomisation scheme; a third-party distributor provided the devices to the study sites.
Was the concealment of treatment allocation adequate?	Yes	Participants, investigators, and study coordinators were blinded to treatment assignment during the randomised phase. An unblinded trainer provided participants with the devices and instructions on device features, proper use, and treatment schedules.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Demographic and baseline characteristics were similar between groups and similar to those reported in other migraine studies.
Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes N/A	
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No N/A	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	All analyses were conducted on the ITT population, which included all participants who were randomly assigned to treatment and provided data for each outcome. Missing data were imputed using the last observation carried forward.

Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York, UK: Centre for Reviews and Dissemination.
Abbreviations: ITT, intent-to-treat; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B45: Critical appraisal of the Goadsby et al (2014) study

Study name	**Goadsby et al (2014)**	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The study was advertised at University of California San Francisco. Additional subjects were enrolled from patients already attending the headache centres (4 US headache centres total). Subjects were recruited between 23 February 2012 and 21 May 2012, and the study was completed by 25 July 2012. The study was approved by institutional review boards appropriate to the investigators. The study was performed under an Investigational Device Exemption (United States Food and Drug Administration; G110224) and registered as NCT01532830.

Study name	Goadsby et al (2014)	
Study question	**Response**	**How is the question addressed in the study?**
Was the exposure accurately measured to minimise bias?	Yes	Subjects were asked to treat up to 4 acute migraine attacks with the device within 6 weeks.
Was the outcome accurately measured to minimise bias?	Yes	Efficacy outcomes were based on the first attack alone and then on all attacks, to minimise bias, to test the hypothesis that the pain-free rates would be clinically relevant to support placebo-controlled trials.
Have the authors identified all important confounding factors?	Not clear	Authors identified inherent confounding factors of open-label and uncontrolled studies, but nothing else.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Placebo-effect data from device-related headache studies were discussed in relationship to the efficacy outcomes.
Was the follow-up of patients complete?	Not clear	
How precise (e.g. in terms of confidence interval and *P*-values) are the results?	N/A	Outcomes were reported as number of AEs (primary) and percentage of attacks achieving pain-free and pain-relief status.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence−12 questions to help you make sense of a cohort study.
Abbreviations: AE, adverse event; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B46: Critical appraisal of the Rubenstein Engel et al (2015) study

Study name	Rubenstein Engel et al (2015)	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	30 subjects were enrolled at 4 investigational sites in the United States and had 12-lead ECGs at baseline.
Was the exposure accurately measured to minimise bias?	Yes	Subjects self-administered a single 90-second nVNS stimulation to the right side of the neck.
Was the outcome accurately measured to minimise bias?	Yes	Cardiac function was assessed with a 12-lead electrocardiogram during the visit. AEs were categorised according to strict criteria.
Have the authors identified all important confounding factors?	Yes	Any cardiac effects could be associated with electrode placement, variations in vagus nerve anatomy, disease state (e.g. status epilepticus), or modification of vagus nerve susceptibility to chronic stimulation by antiepileptic drugs.
Have the authors taken account of the confounding factors in the design and/or analysis?	No	
Was the follow-up of patients complete?	Yes	Patients were routinely followed up after treatment. One subject was excluded because only 1 ECG reading was taken during the treatment visit.
How precise (e.g. in terms of confidence interval and *P*-values) are the results?	Medium precision	No comparative statistics were used, but SEMs of cardiac function were small.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence−12 questions to help you make sense of a cohort study.
Abbreviation: AE, adverse event; ECG, electrocardiogram; nVNS, non-invasive vagus nerve stimulation; SEM, standard error of the mean.

Table B47: Critical appraisal of the NCT03410628 study

Study name	**NCT03410628 (Terminated)**	
Study question	**Response**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	Subjects who were considered had a diagnosis and documented history at least 2 episodes of acute headache pain and allodynia associated with migraine per month, but no more than 15 headache days per month. Subjects were screened for study eligibility and consented to study participation at presentation to the headache clinic.
Was the exposure accurately measured to minimise bias?	Yes	Each subject treated up to 3 migraine headaches with nVNS at home over a period of up to 6 weeks.
Was the outcome accurately measured to minimise bias?	Yes	Subjects completed headache pain scores using a 4-point scale (wherein 3=severe, 2=moderate, 1=mild, and 0=no pain) at baseline (0 minutes) and 120 minutes.
Have the authors identified all important confounding factors?	No	
Have the authors taken account of the confounding factors in the design and/or analysis?	No	
Was the follow-up of patients complete?	No	Follow-up was not completed for 6 of 21 patients because this study was terminated by the sponsor to initiate and focus on larger-scale clinical studies in North America and Europe.
How precise (e.g. in terms of confidence interval and *P*-values) are the results?	N/A	Descriptive statistics and population percentages were used.

Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence−12 questions to help you make sense of a cohort study.
Abbreviations: N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

7.7.2 Details of all important adverse events reported for each study

Table B48: Adverse events in the ACT1 study

	Double-blind phase (≤1 month)			***Open-label phase (3 months)***		
	***nVNS*, No. (%) of patients (N = 73)**	***Sham*, No. (%) of patients (N = 77)**	**Relative risk (95%CI)**	***nVNS*, No. (%) of patients (N = 128)**	***Sham*, No. (%) of patients (N = N/A)**	**Relative risk (95% CI)**
Application site reactions						
Burning/ tingling/ soreness/ stinging	2 (2.7)	7 (9.1)	N/A	4 (3.1)	N/A	N/A
Skin irritation/ redness/ erythema	0	9 (11.17)	N/A	2 (1.6)	N/A	N/A

	Double-blind phase (≤1 month)			Open-label phase (3 months)		
	nVNS, No. (%) of patients (N = 73)	Sham, No. (%) of patients (N = 77)	Relative risk (95%CI)	nVNS, No. (%) of patients (N = 128)	Sham, No. (%) of patients (N = N/A)	Relative risk (95% CI)
Musculoskeletal disorders						
Lip or facial drooping/ pulling/ twitching	8 (11.0)	0	N/A	9 (7.0)	N/A	N/A
Nervous system disorders						
Dysgeusia/ metallic taste	0	7 (9.1)	N/A	2 (1.6)	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B49: Adverse events in the ACT2 study

	Double-blind phase (2 weeks)			Open-label phase (2 weeks)		
	nVNS, No. (%) of patients (N=50)	Sham, No. (%) of patients (N=52)	Relative risk (95% CI)	nVNS, No. (%) of patients (N=83)	Sham, No. (%) of patients (N=N/A)	Relative risk (95% CI)
General disorders and administration site conditions						
Application site irritation	2 (4)	0	N/A	1 (1)	N/A	N/A
Application site paraesthesia	2 (4)	1 (2)	N/A	1 (1)	N/A	N/A
Musculoskeletal and connective tissue disorders						
Myalgia	0	1 (2)	N/A	2 (2)	N/A	N/A
Myokymia	0	0	N/A	2 (2)	N/A	N/A
Skin and subcutaneous tissue disorders						
Rash	1 (2)	2 (4)	N/A	0	N/A	N/A
Skin irritation	2 (4)	0	N/A	0	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B50: Adverse events in the de Coo et al (2019) study

	All Study Periods			Treatment Period 2 – N/A		
	nVNS, No. (%) of patients (N=123)	Sham, No. (%) of patients (N=129)	Relative risk (95% CI)	nVNS, No. (%) of patients (N=N/A)	Sham, No. (%) of patients (N=N/A)	Relative risk (95% CI)
Dysgeusia	0	8 (6.2)	N/A	N/A	N/A	N/A
Erythema at treatment site	0	9 (7.0)	N/A	N/A	N/A	N/A

	All Study Periods			Treatment Period 2 – N/A		
	***nVNS*, No. (%) of patients (N=123)**	***Sham*, No. (%) of patients (N=129)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Perioral myokymia during treatment	8 (6.5)	0	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B51: Adverse events in the PREVA study

	All Study Periods			Treatment Period 2 – N/A		
	***SoC+ nVNS*, No. (%) of patients (N=48)**	***SoC*, No. (%) of patients (N=49)**	**Relative risk (95% CI)**	***SoC+ nVNS*, No. (%) of patients (N=N/A)**	***SoC*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Nervous system disorders						
CH attack	1 (2)	5 (10)	N/A	N/A	N/A	N/A
Dizziness	3 (6)	3 (6)	N/A	N/A	N/A	N/A
Headache	4 (8)	1 (2)	N/A	N/A	N/A	N/A
Infections and infestations						
Nasopharyngitis	1 (2)	4 (8)	N/A	N/A	N/A	N/A
Respiratory, thoracic, and mediastinal disorders						
Oropharyngeal pain	3 (6)	1 (2)	N/A	N/A	N/A	N/A
Musculoskeletal and connective tissue disorders						
Neck pain	3 (6)	0	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CH, cluster headache; CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation; SoC, standard of care.

Table B52: Adverse events in the PRESTO study

	All Study Periods			Treatment Period 2 – N/A		
	***nVNS*, No. (%) of patients (N=122)**	***Sham*, No. (%) of patients (N=126)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
General disorders and administration site conditions						
Application site discomfort	3 (2.5)	1 (0.8)	N/A	N/A	N/A	N/A
Application site erythema	0	3 (2.4)	N/A	N/A	N/A	N/A
Application site pain	0	3 (2.4)	N/A	N/A	N/A	N/A
Infections and Infestations						
Influenza	0	3 (2.4)	N/A	N/A	N/A	N/A

	All Study Periods			*Treatment Period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=122)**	***Sham*, No. (%) of patients (N=126)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Nasopharyngitis	2 (1.6)	3 (2.4)	N/A	N/A	N/A	N/A
Nervous system disorders						
Dizziness	0	3 (2.4)	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B53: Adverse events in the PREMIUM study

	All Study Periods			*Treatment Period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=169)**	***Sham*, No. (%) of patients (N=172)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Most common AEs						
Nasopharyngitis	29 (17.2)	17 (9.9)	N/A	N/A	N/A	N/A
Influenza	16 (9.5)	12 (7.0)	N/A	N/A	N/A	N/A
Dizziness	8 (4.7)	4 (2.3)	N/A	N/A	N/A	N/A
Application site pain	6 (3.6)	10 (5.8)	N/A	N/A	N/A	N/A
Oropharyngeal pain	9 (5.3)	7 (4.1)	N/A	N/A	N/A	N/A
Most common ADEs						
Application site pain	5 (3.0)	10 (5.8)	N/A	N/A	N/A	N/A
Dizziness	5 (3.0)	3 (1.7)	N/A	N/A	N/A	N/A
Application site discomfort	7 (4.1)	5 (2.9)	N/A	N/A	N/A	N/A
Application site erythema	3 (1.8)	8 (4.7)	N/A	N/A	N/A	N/A
Application site rash	1 (0.6)	12 (7.0)	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: ADE, adverse device effect; AE, adverse event; CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B54: Adverse events in the EVENT study

	Randomised phase (2 months)			*Open-label phase (6 months)*		
	***nVNS*, No. (%) of patients (N=30)**	***Sham*, No. (%) of patients (N=29)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=48)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Back pain	1 (3)	0	N/A	1 (2)	N/A	N/A
Cervicalgia	0	2 (7)	N/A	0	N/A	N/A
Dental infection/ tooth pain	1 (3)	1 (3)	N/A	1 (2)	N/A	N/A

	Randomised phase (2 months)			*Open-label phase (6 months)*		
	***nVNS*, No. (%) of patients (N=30)**	***Sham*, No. (%) of patients (N=29)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=48)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Eye twitch	2 (7)	1 (3)	N/A	0	N/A	N/A
Facial pain/ numbness	3 (10)	1 (3)	N/A	0	N/A	N/A
Gastrointestinal symptoms	3 (10)	4 (14)	N/A	5 (10)	N/A	N/A
Head pain	0	0	N/A	2 (4)	N/A	N/A
Influenza	1 (3)	0	N/A	1 (2)	N/A	N/A
Low back pain	1 (3)	1 (3)	N/A	5 (10)	N/A	N/A
Paraesthesia	1 (3)	0	N/A	1 (2)	N/A	N/A
Pharyngitis	0	2 (7)	N/A	0	N/A	N/A
Streptococcal infection, throat	1 (3)	0	N/A	1 (2)	N/A	N/A
Treatment site skin reaction	1 (3)	1 (3)	N/A	2 (4)	N/A	N/A
Upper respiratory tract infection	3 (10)	6 (21)	N/A	11 (23)	N/A	N/A
Vaginitis	2 (7)	1 (3)	N/A	0	N/A	N/A
Worsening migraine	1 (3)	2 (7)	N/A	5 (10)	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B55: Adverse events in the Goadsby et al (2014) study

	Open-label phase (6 weeks)			*Time period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=28)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Stiff neck (mild)[a]	4 (14.3)	N/A	N/A	N/A	N/A	N/A
Stiff neck (moderate)[b]	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Neck twitch (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Lip or facial dropping (mild)	2 (7.1)	N/A	N/A	N/A	N/A	N/A
Frequent urination (mild)	4 (14.3)	N/A	N/A	N/A	N/A	N/A
Raspy voice (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Neck redness (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Neck redness (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Neck swelling (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A

	Open-label phase (6 weeks)			*Time period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=28)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Shoulder pain or spasm (moderate)	2 (7.1)	N/A	N/A	N/A	N/A	N/A
Cough, sneeze, fatigue, achy, sinus headache (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Mild confusion for 2 hours (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Dizziness (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Dizziness for up to 60 minutes (mild)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Tinnitus left ear (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Fever: 102ºF (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A
Joint pain (moderate)	1 (3.6)	N/A	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
[a] Mild AEs were defined as noticeable to the patient but do not interfere with routine activity and do not require medical treatment.
[b] Moderate AEs were defined as interfering with routine activity but responsive to symptomatic therapy or rest.
Abbreviations: CI, confidence interval; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B56: Adverse events in the Rubenstein Engel et al (2015) study

	Open-label phase			*Time period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=29)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
ECG findings						
Clinically significant ECG changes	0	N/A	N/A	N/A	N/A	N/A
Meaningful effect on heart rate	0	N/A	N/A	N/A	N/A	N/A
Meaningful effect on PR interval	0	N/A	N/A	N/A	N/A	N/A
Meaningful effect on QTc interval	0	N/A	N/A	N/A	N/A	N/A
Meaningful effect on QRS duration	0	N/A	N/A	N/A	N/A	N/A

	Open-label phase			*Time period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=29)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Cardiac rhythm abnormalities						
Premature atrial contractions	4 (13.8)	N/A	N/A	N/A	N/A	N/A
Premature ventricular contractions	1 (3.4)	N/A	N/A	N/A	N/A	N/A
Atrial arrhythmias	0	N/A	N/A	N/A	N/A	N/A
Ventricular arrhythmias	0	N/A	N/A	N/A	N/A	N/A
Benign sinus arrhythmia	13 (44.8)	N/A	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval; ECG, electrocardiogram; N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

Table B57: Adverse events in the NCT03410628 study

	Open-label phase			*Time period 2 – N/A*		
	***nVNS*, No. (%) of patients (N=21)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**	***nVNS*, No. (%) of patients (N=N/A)**	***Sham*, No. (%) of patients (N=N/A)**	**Relative risk (95% CI)**
Diarrhoea	1 (4.76)	N/A	N/A	N/A	N/A	N/A

Adapted from European Public Assessment Reports published by the European Medicines Agency.
Abbreviations: CI, confidence interval, N/A, not applicable; nVNS, non-invasive vagus nerve stimulation.

7.7.3 Description of all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude)

No AEs or outcomes were found in the MHRA regulatory database. One report was found in the FDA (Maude) database. The event was described as the experience of neck twitching, lymph node and neck swelling, and numbing and inability to move the left arm. These symptoms presented approximately 5 minutes after the patient's sixth nVNS stimulation. The patient went to the emergency department. The manufacturer was unable to gather additional

information from the patient or the patient's doctor's office (because of no response from the patient and HIPAA).

7.7.4 Brief overview of the safety of the technology in relation to the scope

The benign safety profile of nVNS is consistent across studies of primary headache, including randomised controlled trials in episodic and chronic cluster headache. The infrequent, mild/moderate, and transient AEs observed in these trials establish nVNS as a safe and well-tolerated therapy. As confirmed in the Rubenstein Engel et al (2015) study, nVNS is not associated with any cardiac AEs, a previously identified risk of implantable vagus nerve stimulation devices (Ben-Menachem et al. 2015). Cardiac safety for nVNS is further demonstrated by mechanistic data (Oshinsky et al. 2014) and the clinical studies summarised above (Silberstein et al. 2016b, Goadsby et al. 2018, de Coo et al. 2017, Gaul et al. 2016, Tassorelli et al. 2018, Diener et al. 2018, Silberstein et al. 2016a, Goadsby et al. 2014, Rubenstein Engel et al. 2015, NIH - clincalTrials.gov. 2018).

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Technique, rationale, and details on methodology and results for evidence synthesis and/or meta-analysis

Synthesis of evidence from the randomised, double-blind, sham-controlled ACT1 and ACT2 studies of acute nVNS treatment for cluster headache has been conducted in the de Coo et al (2019) pooled analysis, which was identified in the unpublished study search (section 7.1.2). In this analysis, the primary endpoints from ACT1 and ACT2 were evaluated using data pooled from the studies, with both primary endpoints being consistent with the IHS-recommended primary efficacy criterion for acute CH therapy (Lipton et al. 1995). These endpoints were analysed by treatment group in the total pooled population and separately in eCH and cCH subgroups, and pooled data on adverse events were analysed by treatment group only.

Episodic and chronic CH subtypes have distinct ICHD clinical definitions and may have differential responses to acute treatment (Headache Classification Committee of the International Headache Society. 2018, Lipton et al. 1995). The ACT1 and ACT2 studies demonstrated higher nVNS treatment effects in eCH than in cCH, with an interaction test in ACT2 indicating a differential treatment effect between the eCH and cCH subgroups (P=0.04; type 3 test of fixed effects). The studies were not individually powered to confirm any differential effects between the 2 subtypes. The similar study designs and populations of ACT1 and ACT2 and the need for greater statistical power to evaluate differential effects among eCH and cCH comprised the rationale for selecting these 2 trials for pooled evidence synthesis.

Additional details on the identification, selection, methodologies, quality assessment, and results (with 95% CIs) of the ACT1 and ACT2 studies and

the de Coo et al (2019) pooled analysis are described in sections 7.1 through 7.7. No formal statistical tests for heterogeneity were performed, but key differences among the ACT1 and ACT2 patient populations and methodologies are described in section 7.4.3.

7.8.2 Rationale and qualitative review for the inappropriateness of evidence synthesis for the remaining studies

Further formal evidence synthesis is impractical because of the heterogeneity and inconsistent quality among the remaining PREVA, Marin et al (2018), Nesbitt et al (2015), and Trimboli et al (2018) studies of nVNS in cluster headache. Of these studies, PREVA was appraised as having the highest quality and demonstrated that adjunctive preventive nVNS therapy can safely reduce attack frequency and may yield clinical benefits beyond those afforded by SoC treatment. Results were heterogeneous among the 3 observational trials, with the Marin et al (2018) and Nesbitt et al (2015) studies suggesting efficacy of nVNS consistent with that observed in the randomised controlled PREVA study and the Trimboli et al (2018) study reporting a lower success rate of nVNS for refractory cCH than in the larger controlled studies.

The population, intervention, and comparator were similar in the randomised PREVA trial and real-world Marin et al (2018) trial, both focusing primarily on the preventive effects of SoC+nVNS vs SoC alone in cCH, but study designs and sample sizes were considerably different. The PREVA trial (n=97) was critically appraised as a randomised controlled trial, whereas the Marin et al (2018) study (n=30) was critically appraised as an observational trial with moderate precision. The Nesbitt et al (2015) study evaluated eCH and cCH patients, and the Trimboli et al (2018) study evaluated only the cCH subtype. Both of these studies evaluated the acute and preventive effects of nVNS and were appraised as observational trials with low precision. The small sample sizes, unclear accounts of confounding factors, and inconsistencies in efficacy outcomes reported in these 2 studies preclude formal evidence synthesis, despite their evaluations of a similar intervention for patients with refractory cCH. Other study differences are described in section 7.4.3.

All studies that comprehensively reported adverse events appear to be of moderate to high quality and suggest that nVNS is safe and well tolerated, with only infrequent, mild/moderate, and transient AEs observed. Formal evidence synthesis is also impractical for these studies because of the study differences described in section 7.7.1 and the inconsistencies in adverse events reported across trials (section 7.7.2).

7.9 Interpretation of clinical evidence

7.9.1 Statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology

nVNS is effective, safe, and well tolerated when used to prevent and/or abort cluster headache attacks. This is supported by multiple published and unpublished studies identified and summarised throughout section B. nVNS added to patients' existing SoC therapies significantly reduced attack frequency compared with SoC alone in multiple studies, including a randomised controlled study of cCH. Significant efficacy of nVNS for acute pain relief was demonstrated for patients with eCH in sham-controlled trials, with additional abortive benefits on attack severity and duration seen across studies. No significant adverse events from nVNS have been reported in clinical practice or studies in primary headache, and there is no evidence of cardiac risk in the literature. nVNS was able to reduce the use of acute medication in patients with cluster headache, and its benign safety profile allows the flexibility to use standard medications as rescue therapy when needed. The clinical evidence base in cluster headache for nVNS is consistent with its CE mark in the European Union for the acute and/or prophylactic treatment of primary headache and its clearance in the United States for adjunctive use in the preventive treatment of cluster headache and for the acute treatment of pain associated with eCH in adults.

7.9.2 Summary of the strengths and limitations of the clinical-evidence base of the technology

The data set supporting nVNS use for the preventive and acute treatment of cluster headache is substantial, particularly in the context of this extremely debilitating condition, which is often suboptimally treated given the lack of well-controlled studies of approved therapies (Reuter et al. 2019, Robbins et al. 2016). The clinical evidence is based on trials consistent with the stringent IHS guidelines for controlled studies of drug therapies in cluster headache, including the randomised sham-controlled ACT1 and ACT2 trials in acute treatment (Lipton et al. 1995). The preventive evidence base for nVNS

includes one of the only RCTs evaluating the ability of a treatment to prevent/decrease cluster headache attacks. This study met all IHS recommendations except for the use of a sham control, which is challenging in studies of preventive cCH therapies because of the intense pain experienced by these patients and their reticence to participate in sham-controlled trials (Lipton et al. 1995). Among all non-invasive neuromodulation therapies, nVNS was determined to be the most well studied in cluster headache in terms of the number of studies and their scientific rigor (Reuter et al. 2019).

7.9.3 Brief statement on the relevance of the evidence base to the scope, with a focus on the claimed patient- and system-benefits described in the scope

The evidence base supporting nVNS for the acute and preventive treatment of cluster headache is directly relevant to the scope, which focuses on nVNS use by patients after an initial trial of existing SoC options is unsatisfactory. The PREVA and Marin et al (2018) studies are focused on patients with treatment-refractory cluster headache, with the Marin et al (2018) study specifically evaluating real-world use of nVNS by patients in the United Kingdom who previously had inadequate responses or intolerable side effects with at least 3 cluster headache treatments. Refractoriness to preventive therapies was not a requirement of enrolment into the ACT1, ACT2, and Nesbitt et al (2015) studies, but the majority of patients in these 3 studies were already using multiple medications at baseline and are therefore candidates for inclusion in the treatment-refractory population described in the scope.

The studies collectively demonstrate relevant patient benefits of nVNS based on reductions in the frequency, duration, and severity of cluster headache attacks and improvements in quality of life. The safety and flexibility of nVNS further benefit patients and the healthcare system by essentially eliminating the risk of contraindications, interactions with other treatments, and limits on the number of daily self-administrations. The ability of nVNS to reduce abortive medication use in the studies will likely decrease medication-associated adverse events and costs, reflecting an important benefit to the National Health Service. System benefits will be further detailed in the

economic and cost evaluations of section C. The favourable results of the nVNS studies in cluster headache suggest the clinical relevance and probable success of nVNS among the treatment-refractory cluster headache population defined in the scope.

7.9.4 Factors that may influence the external validity of study results to patients in routine clinical practice

In the majority of the studies reported in this submission, patients' self-administration of nVNS was enhanced by the investigators' implementation of appropriate patient training regarding use of nVNS. The training helped with adherence to treatment, an important consideration for efficacy evaluations of any therapy. To ensure external validity, the sponsor will continue to offer free training and related support services for patients who receive gammaCore™ in the United Kingdom.

7.9.5 Criteria that would be used in clinical practice to select patients for whom the technology would be suitable (based on external validity factors identified in 7.9.4)

No exclusionary medical criteria are needed to select patients who are suitable for nVNS. Cluster headache sufferers who seek medical care and have the ability to be trained by a qualified healthcare professional should be able to benefit from the technology. The training programs will be straightforward, requiring a maximum of only 10 minutes, and will be broadly accessible for patients with a basic reading level or higher and through a wide range of formats (e.g. Web, phone).

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data

A systematic literature review was conducted from the following sources to identify studies reporting economic models and cost analyses in cluster headache.

- MEDLINE and Medline in process via PubMed
- EMBASE and EMBASE Alert via ProQuest
- CRD (DARE, NHS EED, HTA)
- www.heoro.com

The database searches were run on 20 March 2019 using the search strategies reported below in Table C1, Table C2, Table C3, and Table C4 and in section 10, appendix 3.

Table C1: MEDLINE, MEDLINE in process via PubMed

Search	Search string	Number of hits
Limits	Publications with abstracts in humans	
1	Cluster Headache[Mesh] OR "cluster headache"[tiab]	2235
2	"Cost-Benefit Analysis"[Mesh] OR "economics" [Subheading] OR economic*[tiab] OR (cost*[tiab] AND (efficacy[tiab] OR effectiveness[tiab] OR benefit[tiab] OR utilit*[tiab] OR minimi*[tiab] OR analys*[tiab]) OR "monte carlo"[tiab] OR markov[tiab] OR ((cost*[tiab] OR economic*[tiab] OR budget*[tiab]) AND model*[tiab]) OR "discrete event simulation"[tiab] OR "technology assessment"[tiab]	410309
3	1 AND 2	60

Table C2: EMBASE, EMBASE alert (via ProQuest)

Search	Search string	Number of hits
Limits	Publications with abstracts in humans	
1	EMB.EXACT.EXPLODE("cluster headache") OR AB,TI("cluster headache")	4227
2	MJEMB.EXACT("pharmacoeconomics") OR (AB,TI((economic* OR cost* OR budget*) AND (model)) OR (AB,TI(cost AND (efficacy OR effective* OR benefit OR utilit*)) OR "monte carlo" OR markov OR "discrete event simulation" OR "technology assessment"))	312222
3	1 AND 2	80

Table C3: CRD database

Search	Search string	Number of hits
Limits	None	
1	"cluster headache"	19

Table C4: Heoro.com database

Search	Search string	Number of hits
Limits	None	
1	Disease: Cluster headache Study type: Economic model studies	5

8.1.2 Inclusion and exclusion criteria used to select studies from the published and unpublished literature

In total, 143 papers were identified through the searches. After removing 36 duplicates, 107 abstracts were screened.

Inclusion criteria for selecting studies for the review are shown in Table C5 below.

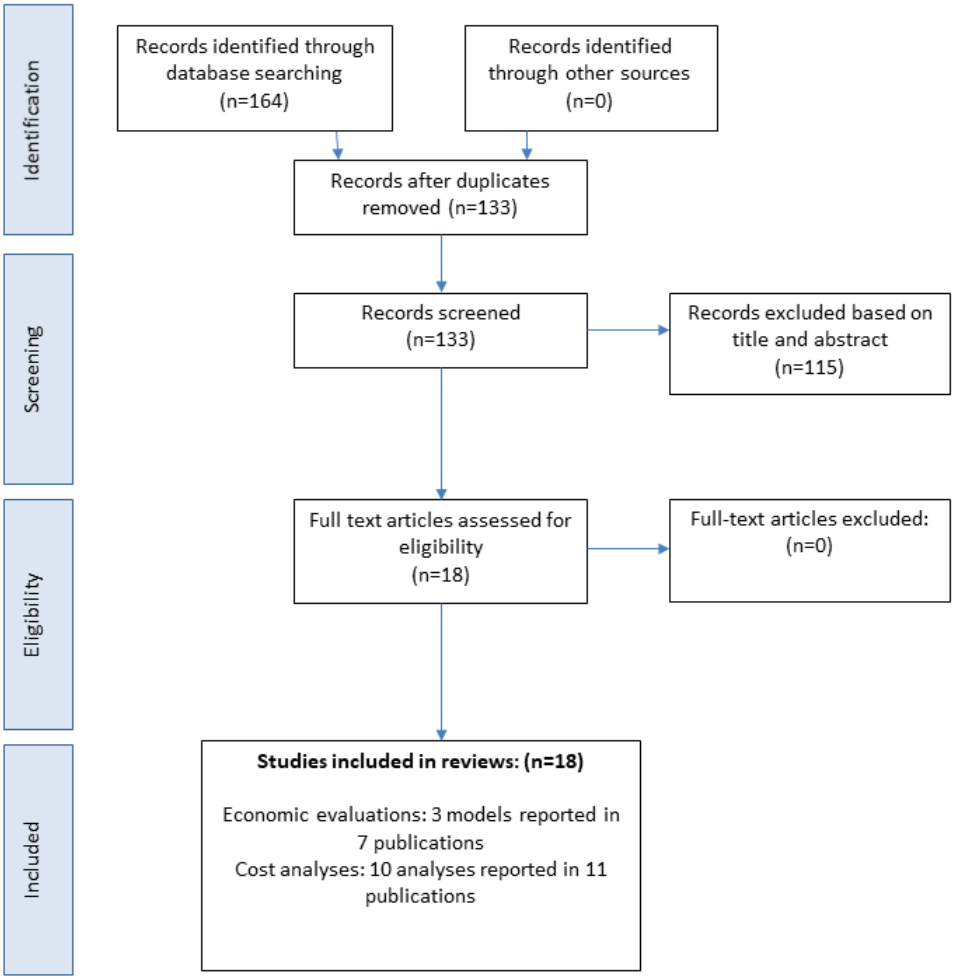
Table C5: Inclusion criteria for the economic model literature review

Criterion	Inclusion criterion	Exclusion criterion
Population	Adults with cluster headache (episodic, chronic or unspecified)	Children with cluster headache; Other types of headache; Mixed populations where <80% of participants have cluster headache; Animal, genetic or other non-clinical or laboratory studies.
Intervention	gammaCore; non-invasive vagus nerve stimulation	
Comparators	Triptans Oxygen therapy (home) Verapamil Sphenopalatine ganglion nerve stimulation Occipital nerve block Placebo or sham procedure Any of the relevant interventions as monotherapy or in combination	Other active controls that are not a relevant intervention.
Outcomes	Cost-utility analysis Cost-effectiveness analysis Cost-benefit analysis Budget impact models Cost analyses	Studies reporting resource use only
Study design	Primary economic evaluations Systematic reviews of economic evaluations Conference abstracts with no corresponding full text publication	Opinion piece articles; Narrative reviews; Case studies with <5 patients; Conference abstracts with corresponding full-text publications.
Language restrictions	No restriction	
Search dates	Databases searched from inception date to 20 March 2019	No date exclusions

8.1.3 Numbers of published studies included and excluded at each stage

The searches identified 133 abstracts after removal of duplicates. Of these, 115 did not meet the inclusion criteria and were excluded. We included 18 publications in the review, seven of which reported on three cost-utility models, and 11 of which reported cost analysis data from 10 studies. The numbers of published studies included and excluded at each stage for this systematic review are shown in Figure C1.

Figure C1: PRISMA diagram



8.2 Description of identified studies

8.2.1 Brief review of each study, including the methods, results, and relevance to the scope

We did not identify any full-text reports of models or cost studies set in the UK. One full publication of a cost-utility model of gammaCore in Germany briefly reported outcomes when the model was re-parameterised for the UK (Morris et al. 2016) and two conference abstracts reported summaries of cost analyses for SPG stimulation (Pietzsch et al. 2017) and occipital nerve stimulation in the UK (Thavaneswaran. 2016).

We identified three high-quality economic evaluations that were reported in seven publications (Table C6). All were cost-utility models with a payer perspective, two for gammaCore, comprising a Markov chain Monte Carlo simulation model of chronic cluster headache in Germany and the UK (Morris et al. 2016) and a decision tree model of episodic cluster headache in the USA (Mwamburi et al. 2017). The third was a decision tree model of sphenopalatine ganglion (SPG) stimulation in chronic cluster headache in Germany (Pietzsch et al. 2015).

The models all compared the main intervention with acute use standard of care (triptans and/or oxygen) and had health states based on whether the patient responded or not to treatment. However, response was defined differently in the three models. In the German/UK gammaCore model, response was defined as having a greater than 50% reduction in cluster headache attacks per week (Morris et al. 2016). The USA gammaCore model defined response as having 50% or more of attacks that responded to gammaCore, and also included a “Failure” health state where 0% of attacks responded within 15 minutes. In this model, non-responders were defined as having 1 to <50% of attacks responding or improved but still needing rescue medication (Mwamburi et al. 2017). In the SPG model, the costs and QALYs were modelled for the intervention and control groups assuming a 31% reduction in attack frequency with the intervention (Pietzsch et al. 2015).

The two gammaCore models had a time horizon of 1 year and therefore did not apply a discount rate. The SPG model had a time horizon of 5 years and applied a 3% discount rate. Efficacy data and utility values were taken from relevant RCTs, but

only one model also used cost and resource use data from the same RCT (Morris et al. 2016), the others basing this on other published cost studies and expert opinion.

All three models found that the intervention dominated standard of care, with probabilistic and deterministic sensitivity analyses or scenarios generally also demonstrating that the intervention was cost-effective at willingness to pay thresholds of €20,000 (Morris et al. 2016) or $25,000 (Mwamburi et al. 2017). The UK gammaCore model was summarised very briefly as a local adaptation of the German model, and found an ICER of £166.12/QALY gained, with 47% of simulations demonstrating cost savings for gammaCore compared with standard of care (Morris et al. 2016).

The eleven cost analyses identified by the systematic review, summarised in Table C7, were as follows:

3 were database analyses of direct costs associated with cluster headache in the USA ((Choong et al. 2018); (Polson et al. 2017); (Ford et al. 2018)), one of which also reported indirect costs (Ford et al. 2018);

1 was a database analysis of direct and indirect costs associated with episodic and chronic cluster headache in Germany (Gaul et al. 2011);

2 reported cost savings and reduction in medication costs following SPG stimulator implantation for chronic cluster headache in Germany (Pietzsch et al. 2018) and the UK (only available as a conference abstract) (Pietzsch et al. 2017);

1 reported costs of different types of oxygen cylinders across the USA as treatment for chronic cluster headache (O'Brien et al. 2017);

3 reported costs associated with occipital nerve stimulation for chronic cluster headache, including 2 in Germany, (Mueller et al. 2013), (Gaul and Müller. 2013) and one conference abstract in the UK (Thavaneswaran. 2016);

1 reported reduction in medication costs after hypothalamic stimulation for chronic cluster headache in Italy (Leone et al. 2009).

These cost analyses found that the direct costs of cluster headache were at least double those of control patients, and were driven by outpatient visits, inpatient admission and medication costs. Chronic cluster headache incurred greater costs than episodic attacks. Costs of medication, in particular subcutaneous triptans, were substantially reduced after nerve or hypothalamic stimulation, with the reduction in some cases being enough to compensate for the implantation costs of the device. Indirect costs due to absenteeism and short-term disability were reported to be approximately 25% to 50% of the direct costs associated with cluster headache.

Details of the economic evaluations are reported below in Table C6 and details of the cost analyses are reported in Table C7.

Table C6: Summary list of published cost-effectiveness studies

	Study		
Parameters	**(Morris et al. 2016)**	**(Mwamburi et al. 2017)**	**(Pietzsch et al. 2015)**
Study objective	To assess whether non-invasive vagus nerve stimulation (nVNS, gammaCore) is a cost-effective treatment option compared with the current standard practice (SoC) for chronic cluster headache in Germany.	To conduct a cost-effectiveness analysis of gammaCore adjunct to SoC compared with SoC alone for the treatment of acute pain associated with episodic cluster headache attacks in the USA.	To assess the cost-effectiveness of sphenopalatine ganglion (SPG) stimulation compared with medical management in Germany.
Study characteristics	**Analyses type:** Cost-utility **Model Structure: P**robabilistic model using a Markov chain Monte Carlo simulation **Patient population:** Patients with chronic cluster headache in Europe (predominantly in Germany) **Tx comparisons:** SoC+nVNS vs SoC **Country:** Germany and UK **Perspective**: German statutory health insurance (payer) **Outcome measure:** ICER for Cost per QALY gained **Time horizon:** 1 year **Cycle length:** NR **Cost yr and currency:** €, year unclear **Discount rate**: NR	**Analyses type:** Cost-utility **Model Structure:** Decision-tree model **Patient population:** Patients with episodic cluster headache **Tx comparisons:** gammaCore nVNS vs SoC **Country:** USA **Perspective**: Payer **Outcome measures:** ICER for Cost per QALY gained **Time horizon:** 1 year **Cycle length:** NR **Cost yr and currency:** 2017, USD **Discount rate**: NR	**Analyses type:** Cost-utility **Model Structure:** Decision tree model **Patient population:** Patients with chronic cluster headache, age 45 years, 84% male **Tx comparisons:** SPG stimulation vs medical management **Country:** Germany **Perspective**: Payer **Outcome measures:** ICER for cost per QALY gained **Time horizon:** 5 year **Cycle length:** NR **Cost yr and currency:** 2014, € **Discount rate**: 3%
Health states	Responders (≥50% reduction from baseline in number of CH attacks per week). Non-responders (<50% reduction in CH attacks).	Failures (lack of adherence or lack of efficacy; 0% of attacks responded fully within 15 minutes). Non-responders (1% to 50% of attacks responded; reduced duration and/or intensity of treated attacks but still needing rescue medication). Responders (≥50% of attacks responded).	Responders (pain relief within 15 minutes of onset of attack without rescue medication). Non-responders (not defined).

	Study		
Parameters	**(Morris et al. 2016)**	**(Mwamburi et al. 2017)**	**(Pietzsch et al. 2015)**
Model assumptions	Beyond the 4-week randomised phase, responders in the SoC group were assumed to be non-responders, and non-responders in the SoC+nVNS group were assumed to discontinue prophylactic treatment with nVNS but continue use of abortive treatments. Patients who were responders throughout the 4-week study extension period were assumed to maintain this response until the end of the model time horizon (1 year). Patients in the SoC+nVNS group who maintained responder status were assumed to continue using the same amount of resources as those observed in the overall SoC+nVNS group during the randomised phase. Non-responders were assumed to have the same resource use as that observed in the SoC group during the randomised phase. Scenario analyses assumed either an exponential decrease in response over time; or that this rate of decrease in response decreased by 10% per month, or that SoC group did not respond.	The model assumed 3 prescriptions per seasonal bout. Failures have no change in utilities, do not need prescriptions for additional devices and costs are the same as for SoC. Non-responders may return to provider and receive retraining; some will improve and others will stop after 2nd device. Assumed 6 prescriptions for gammaCore would be needed per year (conservative estimate, 4 or 5 may be more realistic). Base case used data from pooled analysis of 2 RCTs, sensitivity analyses used data from 1 RCT as lower and the other RCT as upper limits. Sensitivity analyses varied parameter estimates for treatment effects, costs and utilities.	All chronic CH attacks not successfully treated with SPG stimulation would be treated with standard medical management at average doses; successfully treated attacks need no rescue medication. Stimulation would reduce the average frequency of chronic CH attacks in the SPG-treated cohort by 31% based on Pathway CH-1 study. Effectiveness of SPG assumed to remain constant over time and based on Pathway CH-1 study outcomes. Prophylactic effect would gradually decline by 10% each year across cohort of responders and non-responders. Resource use and utilities remain constant in the medical management group throughout the analysis and are taken from baseline data in the Pathway CH-1 study. Medical management group maintain baseline attack frequency. Assume utilities at 3 to 5 years are the same as projected values for 12 to 24 months.
Efficacy data	Data from PREVA study.	Data from pooled analysis of the ACT1 and ACT2 trials with data from the meta-analysis providing the base case parameters. Effective probabilities of being a responder or partial response were based on insights from literature and patient experiences.	Data from the Pathway CH-1 study.

	Study		
Parameters	**(Morris et al. 2016)**	**(Mwamburi et al. 2017)**	**(Pietzsch et al. 2015)**
Model inputs	**Resource use:** Data on abortive medication use (to end an attack: intranasal (IN) zolmitriptan, subcutaneous (SC) sumatriptan, inhaled oxygen) taken from the last 14 days of the PREVA randomised phase. **Costs:** nVNS use cost was the listed price in Germany, unit costs for IN zolmitriptan and SC sumatriptan were determined from the Lauer-Taxe. Costs for inhaled oxygen were derived using the estimated daily cost for oxygen from a previous study and data from the baseline phase of PREVA. **Utility values:** EQ-5D index scores from the PREVA study, estimated for responders and non-responders using the German tariff: • SoC+nVNS responder utility = 0.772 • SoC+nVNS nonresponder utility = 0.536 • SOC responder utility = 0.760 • SoC nonresponder utility = 0.523	**Resource use:** based on literature and patient experiences. **Costs:** Cost data were derived from Polson et al and expert opinion. **Utility values:** EQ-5D health index values from ACT2 trial. **Utilities in base case**: Responders = 0.90 ± 0.048 Non-responders = 0.71 ± 0.038 Failures = 0.71 ± 0.038	**Resource use:** Resource use data taken from a prior resource use and costing study on patients with chronic cluster headache in Germany (Gaul 2011). **Costs:** Unit costs of medication from Rote List from 2014; SPG stimulation costs from DRG reimbursement amounts for 2014, manufacturer and author estimates and Gaul 2011 study. Did not include costs of preventive medication. **Utility values:** Summary scores of SF-36v2 from Pathway CH-1 study and mapping algorithm to EQ-5D values. Baseline = 0.548 Stimulation cohort: End of experimental phase (3 to 8 weeks after implantation and therapy titration) = 0.668 Open label phase (to end of year 1) = 0.675 12 months = 0.614 24 months = 0.683 Years 2 to 5 = 0.61
QALYs (mean) (overall)	SoC+nVNS = 0.607 SoC alone = 0.522 **Additional analysis for UK (reported briefly):** SoC+nVNS = 0.538 SoC = 0.438	SoC+nVNS = 0.83 SoC alone = 0.74	SPG cohort: QALY gain = 0.086 (year 1), 0.066 (years 2 to 5). Resulting discounted QALY gain over 5 years was 0.325. QALYs over 5 years (discounted): SPG group = 2.87, control group = 2.55, difference = 0.32. QALYs over 5 years (undiscounted): SPG group = 3.09, control group = 2.74, difference = 0.35.

	Study		
Parameters	**(Morris et al. 2016)**	**(Mwamburi et al. 2017)**	**(Pietzsch et al. 2015)**
Costs (Treatment, Description, Cost per dose)	**Costs per dose:** **IN zolmitriptan** = €14.07 **SC sumatriptan** = €31.31 **Inhaled oxygen** = €2.87 **nVNS** (gammaCore device pre-loaded with 300 stimulations) = €0.87 **Mean expected costs:** SoC+nVNS = €7096.69 SoC = €7511.35 Overall abortive medication costs were 23% lower in the SoC+nVNS group than in the SoC alone group. Compared with the SoC alone group the SoC+nVNS group had 29% lower SC sumatriptan costs, 19% lower inhaled oxygen costs and 75% higher IN zolmitriptan costs. **Additional analysis for UK: mean costs** SoC+nVNS = £5409.83 SoC = £5393.31	Cost per gammaCore prescription = $590 Overall annual cost of care with SoC = $10,040 ± $490. Mean annual costs for SoC+nVNS reported both as $9660 and $9510 for base-case. Mean costs for SoC reported both as $10,020 and $10,040 for base-case.	**Medication costs:** Mean medication cost per attack = €8.92 **SPG stimulation costs:** Implantation of SPG stimulation system (hospital inpatient) = €5,293.99 Reimbursed cost of ATI SPG Neurostimulator = €25,000.00 CT/CVT imaging cost pre- and post-implant = €400.00 6 visits to headache centre for device titration, follow-up to implantation = €596.46 Revision of implant (4 of 32 patients) = €5,293.99 Antibiotics for infection (3 of 32 patients) = €94.88 Device explantation, without new implantation (2 of 32 patients, outpatient) = €355.77 **Base case** 5-year costs, discounted: SPG = €42,187 Control = €41,298 5-year costs, undiscounted SPG = €42,998 Control = €44,475

	Study		
Parameters	**(Morris et al. 2016)**	**(Mwamburi et al. 2017)**	**(Pietzsch et al. 2015)**
Results (incremental cost effectiveness ratio)	**Base case**: ICER = nVNS dominant over SoC. Approximately 80% of probabilistic simulations generated cost savings, most had an ICER< €20,000/QALY gained. **Alternative scenarios analyses:** • Constant rate of response loss (31% reduction in response per month); • Diminishing rate of response loss (rate of reduction in response decreased by 10% per month); • No response for SoC group. For all 3 scenarios, nVNS was dominant over SoC (ICER). **Probabilistic Sensitivity Analysis** (1,000 simulations for each scenario, to calculate % of simulations that resulted in cost savings): • Constant response loss: 71% were cost-saving; • Diminishing rate of response = 79% were cost-saving; • No response for SoC = 79% were cost-saving. **Additional analysis for UK** Base case = £166.12/QALY gained. 47% of simulations demonstrated cost-savings for nVNS vs SoC.	**Base case:** gammaCore dominant over SoC. ICER ($/QALY): Not estimated (difference = –$5890/QALY). **Sensitivity analyses:** Probabilistic = 100,000 Monte Carlo simulations. Deterministic analyses used high and low value estimates for costs, probabilities of being in each health state, utility values, cost reduction factor due to gammaCore and number of gammaCore prescriptions per year. All 1-way and multiway **sensitivity analyses** were cost-effective using a threshold of $25,000. >95% were cost-effective at WTP threshold of $20,000. Main drivers were cost reduction factor, number of prescriptions per year and cost of SoC.	**Base case, 5 years, discounted:** ICER = €2736/QALY, **Base case, 5 years, undiscounted:** ICER = <0; SPG dominating. Overall savings at 5 years = €2736 **Sensitivity analyses:** Varied pain relief rates, number of attacks per day, cost of medications, frequency reduction, change in frequency response, time horizon; use of subcutaneous sumatriptan; Payer to fund stimulation device for revisions. ICER ranged from SPG dominating to €50,590/QALY.

Abbreviations: CH, cluster headache; ED, emergency department; ICER, incremental cost-effectiveness ratio; ONS, occipital nerve stimulation; NR, not reported; nVNS, non-invasive vagus nerve stimulation; QALY, quality-adjusted life-year; SoC, standard of care; SPG, sphenopalatine ganglion stimulation; Tx, treatment.

Table C7: Summary list of all evaluations involving costs

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Choong et al (2018); United States				
Cost analysis of health care resource utilization and direct costs associated with cluster headache (CH) compared with controls.	Adults with cluster headache (any type) from the Truven Health Analytics MarketScan Research Database diagnosed between 2010 to 2013; N = 6,562 Approximately 20 controls matched to each case from patients with no ICD-9 diagnosis of headache; N=143,761. **Age (Mean ± SD)** CH= 47.1 yr ± 13.3 Control = 47.9 yr ± 13.4 **Gender:** CH = 3,890 male (59.3 %) **Control:** 80,830 male (56.2%)	**Outpatient visits** (Mean ± SD)**:** **CH**: % with any visit = 100%; Number of visits = 26.49 ±26.46 cost = $8,052±16,470 **Controls**: % with any visit = 96.4%; Number of visits = 12.40 ±16.28 costs = $3,783 ±14,393, *P*<0.001 **Inpatient admissions** (Mean ± SD): **CH**: % with any admission = 14.8%; Number of admissions = 0.22 ±0.69 costs = $ 4,467 ± 28,121 **Controls**: % with any admission = 6.1%; Number of admissions = 0.08 ±0.36 costs = $1,720 ± 16,331, *P*<0.001 **Neurology** (Mean ± SD)**:** **CH**: % with any visit = 45.2%; Number of visits = 1.57 ±2.78 costs = $341± 1078 **Controls**: % with any visit = 3.3%; Number of visits = 0.08 ±0.62 costs = $23 ± 445, *P*<0.001	Did not report changes in cluster headache frequency or severity. **Main reasons for attending ED**: Gastric ulcer: CH = 7.1%; Control = 0.18% Chest pain: CH = 4.0%; Control = 2.3% Subarachnoid haemorrhage: CH = 3.6%; Control = 0.15% Cerebral artery occlusion: CH = 3.1%; Control = 1.6% Migraine with aura: CH = 2.5%; Control = 0% Syncope/collapse: CH = 2.1%; Control = 1.1% Diverticulitis of colon: CH = 2.1%; Control = 1.3% Headache: CH = 2.0%; Control = 0.13% Coronary atherosclerosis: CH = 1.9%; Control = 2.7% Subendocardial infarction: CH = 1.9%; Control = 3.0% **Main reasons for admission**: Chest pain: CH = 2.1%; Control = 1.4% Rehabilitation: CH = 2.1%; Control = 1.5% Cerebral artery occlusion: CH = 1.9%; Control = 1.0% Pneumonia: CH = 1.7%; Control = 2.0% Coronary atherosclerosis: CH = 1.7%; Control = 2.7% Osteoarthrosis, lower leg: CH = 1.7%; Control = 2.9% Headache: CH = 1.6%; Control = 0.06% Syncope/collapse: CH = 1.5%; Control = 0.6% Diverticulitis of colon: CH = 1.3%; Control = 1.0% Osteoarthrosis pelvis and thigh: CH = 1.2%; Control = 1.4%	**Total costs** (Mean ± SD, USD)**:** CH = $16,530±40,068 Controls = $7,197±25,147 Approximate total direct cost for CH is greater than $2.8 billion/year for whole US population of 2014. Main driver of costs was outpatient visits followed by inpatient admissions.

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Choong et al (2018); United States (cont'd)				
		Radiology (Mean ± SD)**:** **CH**: % with any service = 76.5%; Number of visits = 3.55 ±5.23 costs = $1418 ± 3236 **Controls**: % with any service = 52.1%; Number of visits = 1.66 ±3.14 costs = $483 ± 2381, *P*<0.001 **Pharmacy** (Mean ± SD): **CH**: % with any claims = 78.2%; costs = $2,509 ± 6557 **Controls**: % with any claims = 73.1%; costs = $1,319 ± 5105, *P*<0.001 **ED** (Mean ± SD): **CH**: % with any visits = 36.9%; Number of visits = 0.98 ±2.76 costs = 1,502 ± 6,322 **Control**: % with any visits = 16.2%; Number of visits = 0.25 ±0.79 costs = 376 ± 1,892, *P*<0.001		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Choong et al (2018); United States (cont'd)				
		Laboratory costs (Mean ± SD) **CH**: % with any service = 8.3%; Number of visits = 3.75 ±25.83 costs = NA **Controls**: % with any service = 5.8%; Number of visits = 2.08 ±14.57 costs = NA **Total costs in 12 months before first diagnosis of CH (2014 costs),** Mean ± SD (USD) **CH:**12,359 ± 27,251 **Control:** 6,552 ± 21,088		
Polson et al (2017); United States				
Cost analysis comparing healthcare use and total cost in patients suffering from cluster headaches (CH) with patients without headache-related conditions.	Adults with diagnosis of chronic, episodic or undefined cluster headache enrolled in a Medicare or commercial health plan first diagnosed in 2009 to 2015; propensity score-matched controls with no headache diagnoses. CH cohort: overall mean age = 47 yr 48% male Mean Charlson Comorbidity Index = 0.3	**Resource use per patient by medical service type,** number of patients (%) **Episodic CH** Diagnostic testing = 715 (95.2%) ED visits = 366 (48.7%) Home infusion/specialty treatment = 148 (19.7%) Hospital inpatient admission = 160 (21.3%) Hospital outpatient visit = 599 (79.8%) Physician office visit = 748 (99.6%)	Changes in CH frequency or severity NR	**Overall medical costs per patient,** mean ± S.D (median)**:** **CH overall = $**25,805 ± 45,650 ($12,225) **Episodic CH =** $22,607 ±39,721 ($12,158) **Chronic CH =** $30,502 ± 50,131 ($15,091) **Undefined CH =** $25,436 ± 45,851 ($11,553) **Control =** $10,140 ± 39,412 ($3,383)

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Polson et al (2017); United States (cont'd)				
	Episodic CH = 18% of CH cohort Chronic CH = 17.3% Undefined = 64.7%	**Chronic CH** Diagnostic testing = 697 (96.3%) ED visits = 361 (49.9%) Home infusion/specialty treatment = 191 (26.4%) Hospital inpatient admission = 175 (24.2%) Hospital outpatient visit = 609 (84.1%) Physician office visit = 716 (98.9%) **Undefined CH** Diagnostic testing = 2583 (95.7%) ED visits = 1424 (52.8%) Home infusion/specialty treatment = 478 (17.7%) Hospital inpatient admission = 565 (20.9%) Hospital outpatient visit = 2214 (82.0%) Physician office visit = 2649 (98.1%) **Controls** Diagnostic testing = 3231 (77.4%) ED visits = 962 (23.0%) Home infusion/specialty treatment = 427 (10.2%) Hospital inpatient admission = 253 (6.1%) Hospital outpatient visit = 2141 (51.3%) Physician office visit = 4089 (98.0%) **Number of prescription fills per patient**, mean ± S.D (median) **CH overall =** 25.66 ± 21.04 (20) **Episodic CH =** 23.90 ± 19.09 (19) **Chronic CH =** 30.66 ± 23.23 (25) **Undefined CH** = 24.79 ± 20.74 (19) **Control =** 12.34 ± 11.33 (9)		Main contributors to pharmacy costs were analgesics (63.8% of all CH patients), opiates (53.9% of all CH patients), oral triptans (25.2% of all CH patients) valproate (25.2% of all CH patients).

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Polson et al (2017); United States (cont'd)				
		Costs per patient mean ± S.D (median) **CH total cohort:** Diagnostic Testing (n=3995) = $3857 ± 5321 Emergency Department (n=2151) = $1986 ± 5095 Home Infusion/Specialty Rx (n=817) = $4977 ± 44,470 Hospital Inpatient (n=900) = $7312 ± 16,736 Hospital outpatient (n=3422) = $12,459 ± 25,328 Physician Office (n=4113) = $7379 ± 13,843 **Control:** Diagnostic Testing = 1515 ± 3160 Emergency Department = 1268 ± 2044 Home Infusion/Specialty Rx = 1730 ± 8450 Hospital Inpatient = 8528 ± 45,509 Hospital outpatient = 7644 ± 45,146 Physician Office = 3672 ± 9495 **Overall prescription cost per patient** mean ± S.D (median) **CH overall = $**9197 ± 19,839 ($2947) **Episodic CH = $**8209 ± 17,353 ($3095) **Chronic CH = $**12,534 ± 21,528 ($5497) **Undefined CH** = 8570 ± 19,913 ($2477) **Control = $**4368 ± 13,379 ($891)		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Ford et al (2018); United States				
Cost analysis of direct and indirect costs of cluster headache (CH)	Adults aged 18 to 64 years diagnosed with cluster headache (any type) between 2009 and 2014. N=18,303 (9,328 with direct cost data) Mean (SD) age = 44.6 (11.1) years Gender: Male = 61.4% Patients had to have had at least 2 non-diagnostic claims at least 30 days apart with cluster headache diagnosis. Comorbid diseases of interest with >5% frequency included migraine (28.9%, n=2,693), hypertension (18.0%, n=1,683), hyperlipidaemia (14.2%, n=1,327), depression/suicide/self-harm (9.3%, n=871), sleep disorders (9.2%, n=857), anxiety (7.9%, n=739), and chronic pulmonary disease (6.9%, n=647).	Data from patients in the Truven Health Analytics Marketscan Commercial and Health and Productivity Management Research Databases Costs converted to 2015 $ **Healthcare utilisation by CH cohort, % with each contact per year** Inpatient admission = 23.3% all-cause, 11.2% CH-related ED visit = 46.6% all-cause, 10.5% CH-related HCP office visit = 99.4% all-cause, 81.5% CH-related Laboratory test = 91.4% all-cause, 19.9% CH-related Hospital outpatient visit = 73.4% all-cause, 16.7% CH-related Other outpatient visit = 96.2% all-cause, 34.5% CH-related Pharmacy fulfilment = 97.1% all-cause, 87.3% CH-related CH-related procedures = 0% all-cause, 21.8% CH-related **Direct cost of healthcare per patient per year** **All-cause annual costs, mean (SD)** Inpatient admission: $5,201 (25,970) Emergency room: $808 (3,115) Healthcare provider office visit: $1,071 (1,055) Laboratory test: $652 (1,886) Hospital outpatient visit $3,631 (10,926)	Data on cluster headache frequency or severity NR	**All-cause costs Mean (SD)** Total annual cost: $17,574 (40,970) (Largest contributors were inpatient admissions =$5201, outpatient visits =$3631, prescriptions = $3265, outpatient services = $2947, office visits = $1071) **Cluster headache-related costs Mean (SD)** Total annual cost: $3,132 (13,396) (Largest contributors were inpatient admissions =$1604, prescriptions = $809) **Indirect costs for patients per patient per year, mean (SD)** Patients with absenteeism data = $4,928 ($4,860) Patients with short-term disability claims = $803 ($2,621) Patients with absenteeism + short-term disability data = $3,374 ($3,198)

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Ford et al (2018); United States (cont'd)				
		Other outpatient services: $2,947 (14,902) Pharmacy fulfilment: $3,265 (7,302) Cluster headache procedure: NR **Cluster headache-related annual costs, mean (SD)** Inpatient admission: $1,604 (13,004) Emergency room: $88 (520) Healthcare provider office visit: $201 (255) Laboratory test: $25 (160) Hospital outpatient visit: $193 (1,165) Other outpatient services: $95 (1,009) Pharmacy fulfilment: $809 (2,226) Cluster headache procedure: $114 (377) **Productivity losses** **Number with work-hours lost per year** • 77.7% of patients with absenteeism data (129/166) • 23.0% of patients with short-term disability (194/844) • 81.3% of patients with absenteeism + short-term disability (113/139) **Number of hours lost per person per year, mean (SD)** • Patients with absenteeism data = 224.0 (220.9) • Patients with short-term disability data = 60.8 (198.6) • Patients with absenteeism + short-term disability data = 255.6 (242.2)		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Gaul et al (2011); Germany				
Cost analysis of direct and indirect costs of cluster headache.	Adults in a single tertiary centre with chronic or episodic cluster headache in 2010. N=179, 46.7% episodic **Mean age:** All CH = 44.7 ± 11.2 years Episodic CH = 44.5 ± 10.8 years Chronic CH = 45.0 ± 11.8 years **Gender male:** All CH = 126/179 (70%) Episodic CH = 82 (60.3%) Chronic CH = 54 (39.7%) **Duration of disease, mean** All CH = 12.9 years Episodic CH = 14.0 years Cluster CH = 11.3 years	Data collected via questionnaire. Costs calculated for 6 months following index diagnosis and adjusted to 2010 € costs. **Resource use** **Attack-aborting medication:** Episodic CH = 61.7% of patients Chronic CH = 91.7% of patients **Prophylactic medication use:** Episodic CH = 57% Chronic CH = 87.5% **Outpatient headache clinic visits:** Episodic CH = 38.3% of patients, mean 1.9 visits, range 1 to 8 visits Chronic CH = 73.6% of patients, mean 1.8 visits, range 1 to 6 visits **Neurologist visits:** Episodic CH = 8.4% of patients, mean 3.7 visits Chronic CH = 26.4% of patients, mean 4.4 visits **GP visits:** Episodic CH = 20.6% of patients, mean 7.6 visits Chronic CH = 26.4% of patients, mean 12.4 visits **Neurosurgeon visits:** Episodic CH = 1% of patients, 2 visits Chronic CH = 5.6% of patients, mean 1.8 visits **Pain specialist visits:** Episodic CH = 1% of patients, 5 visits Chronic CH = 8.3% of patients, mean 7.3 visits	**Mean number of attacks per day:** Episodic CH = 3.3 Chronic CH = 3.8 Range 1 to 12 attacks per day. **Mean duration of bouts** = 10.6 weeks (range 1 week to 6 months).	**Total Costs per patient per 6 months:** **All CH** Direct costs = €4737 Indirect costs = €1226 All costs = €5963 **Chronic CH** Direct costs = €9073 Indirect costs = €1912 All costs = €10,985 **Episodic CH** Direct costs = €1819 Indirect costs = €764 All costs = €2583

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Gaul et al (2011); Germany (cont'd)				
		Reimbursement costs (privately insured patient per visit, first visit): Headache centre: €100.71 Neurologist: €100.71 GP: €30.60 Neurosurgeon: €48.03 Pain specialist: NA **Reimbursement costs (insurance for 3-month period):** Headache centre: €92.84 Neurologist: €31.54 GP: €31.54 Neurosurgeon: €31.54 Pain specialist: €58.71 **Cost of attack-aborting treatment:** **All CH, per patient per 6 months:** Oxygen: €416 Zolmitriptan nasal spray: €2571 Sumatriptan s/c: €11,556 Sumatriptan nasal spray: €1459 **Chronic CH, per patient per 6 months:** Oxygen: €533 Zolmitriptan nasal spray: €4318 Sumatriptan s/c: €14,457 Sumatriptan nasal spray: €3044 **Episodic CH, per patient per 6 months:** Oxygen: € 334 Zolmitriptan nasal spray: €1790 Sumatriptan s/c: €8901 Sumatriptan nasal spray: €1332		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Gaul et al (2011); Germany (cont'd)				
		Cost of prophylactic medication: **All CH, per patient per 6 months:** Verapamil: €134 Lithium: €79 Topiramate: €180 Melatonin: €1290 Gabapentin: €330 Valproate: €86 Steroid pulse therapy: €113 Occipital nerve block: €16 **Chronic CH, per patient per 6 months:** Verapamil: €175 Lithium: €80 Topiramate: €227 Melatonin: €1290 Gabapentin: €413 Valproate: €93 Steroid pulse therapy: €139 Occipital nerve block: €16 **Episodic CH, per patient per 6 months:** Verapamil: €96 Lithium: €78 Topiramate: €110 Melatonin: NR Gabapentin: €248 Valproate: €42.12 Steroid pulse therapy: €99.73 Occipital nerve block: €15		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Pietzsch et al (2018); Germany				
Cost analysis to estimate annual costs of preventive and acute medications for patients with sphenopalatine ganglion stimulation (SPG) compared with usual care.	Patients with chronic cluster headache N=71 Mean (SD) age = 49 (±12) Female, % (±SD) = 27 (±24)	Cost data in 2016 € taken from the Pathway R1 Registry of patients with SPG microstimulators in Germany, Austria and Denmark. **Annualized mean medication costs** (calculated from the reported medication use for the previous 4 weeks at 3, 6, 9 and 12-month follow-up visits): **3 months =** €5928 ± 12,668 **6 months =** €5229 ± 12,442 **9 months =** €4098 ± 8151 **12 months =** €6662 ± 13,711 **Annualised median medication costs:** **3 months =** €1745 **6 months =** €713 **9 months =** €353 **12 months =** € 1092 SPG stimulator device plus implantation = €32,000	Mean baseline attack frequency (per week): 24±18 **Attack frequency after SPG stimulation:** Baseline = 100% 3 months = 56% 6 months = 68% 9 months = 61% 12 months = 63%	Main cost drivers are acute medication costs. **Annual medication cost:** **Baseline (no SPG stimulation):** Mean acute medication cost = €14,178 Mean preventive medication cost = €559 Mean total medication costs = €14,737 ± 18,918; Median total medication costs = €6061 **With SPG stimulation:** Mean acute medication cost = €6,342 Mean preventive medication cost = €328 Mean total medication costs = €7,253 Mean change in annual estimated total drug cost = €7484± 14,574, 51% reduction from baseline Median drug cost reduction = €3002 5-year undiscounted mean medication cost savings = €37,422

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Pietzsch et al (2018); Germany (cont'd)				
				5-year medication cost savings (discounted at 5%) = €35,305
Pietzsch et al (2017); United Kingdom				
Cost analysis to estimate reduction in medication costs in patients with sphenopalatine ganglion stimulation (SPG) compared with usual care.	Patients with chronic cluster headache N = 71	Resource use taken from the Pathway R1 Registry of patients with SPG microstimulators in Germany, Austria and Denmark Costs based on 2017 BNF drug costs using the lowest priced product and largest available package size. Weekly medication costs: Baseline = £197.60 12 months after ONS = £89.42 (54.8% reduction) Saving = £108.20	NR (abstract only)	**Annualised medication costs** (assuming steady-state) Baseline = £10,276 12 months after ONS = £4,650 Saving = £5,626
O'Brien et al (2017); United States				
Cost analysis for inhaled oxygen as acute medication for cluster headache in the USA.	Patients with episodic or chronic cluster headache.	Cost data were taken from market research on the most recent price lists and product catalogues. **E Type oxygen tank (for wheelchair use):** Upfront cost: $0 to $175 Monthly rental: $0 to $45 Oxygen refill cost: $0 to $45 High-flow regulator upfront cost: $0 to $45 High-flow regulator monthly rental cost: $0 to $110 Non-rebreather mask upfront cost: $0 to $36, most = $3 to $6 Non-rebreather mask monthly rental cost: $0 to $5 a month	**Episodic**: Assumed 6-week duration of exacerbation; 2 exacerbations per year; 1.5 attacks per day. **Chronic**: Assumed 7-week duration of exacerbation 7 exacerbations per year 1.5 attacks per day. Did not model changes in cluster headache frequency or severity.	**For patients with episodic CH:** Annual cost of high-flow oxygen therapy <$1000 in 38 US states. Of these 38 states, annual cost <$500 in 28 states. **For patients with chronic CH:** Annual cost of high-flow oxygen therapy (in 39 states) <$5000 in 39 states. Of these 39 states, annual cost <$2000 in 28 states.

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
O'Brien et al (2017); United States (cont'd)				
Assumed oxygen is administered via a non-rebreather face mask at 10 L/minute for 15 minutes per attack.		**H Type oxygen tank (not portable):** Upfront cost: $0 to $375 Monthly rental: $0 to $45 Oxygen refill cost: $0 to $50 High-flow regulator upfront cost: $0 to $36 High-flow regulator monthly rental cost: $0 to $75 Non-rebreather mask upfront cost: $0 to $18, most = $2 to $5 Non-rebreather mask monthly rental cost: $0 to $10 a month **M Type oxygen tank (description NR):** Upfront cost: $0 to $250 Monthly rental: $0 to $110 Oxygen refill cost: $0 to $50 High-flow regulator upfront cost: $0 to $90 High-flow regulator monthly rental cost: No rental costs/included in total costs Non-rebreather mask upfront cost: $0 to $23 Non-rebreather mask monthly rental cost: No rental costs/included in total costs		

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Mueller et al (2013); Gaul and Müller (2013); Germany				
Cost analysis of occipital nerve stimulation (ONS) for the treatment of chronic cluster headache (CH)	Patients with chronic cluster headache (n=24) or chronic migraine (n=3) treated at one centre with ONS between 2008 and 2012. Mean age = 30 years Male = 18 Patients all had daily attacks without attack-free periods for >4 weeks per year despite prophylactic medication.	Costs and resource use from clinical records and DRG reimbursement prices. **Direct hardware-related costs (27 patients):** **Total:** €506,019 Leads (n=62) = €67,182 Extension kits = 39,590 IPGs (n=30) = €378,907 Patient programmer = €20,340	CH: Mean 5 attacks per day at baseline (range 1 to 14); Mean pain score = 8/10; Mean 1.5 triptan doses/day. 2/24 patients with CH failed to respond 1/24 failed to respond to CH but associated migraine improved. CH: mean 3 attacks per day after ONS (range 0 to 8) Mean 0.9 triptan doses/day. **Overall response rate:** 89% at 3 months 78% at mean 20-month follow-up	**Overall costs for all 27 patients** Hospitalisation = €255,024: • Trial period costs = €109,296 • Implantation (n=25) = €101,200 • Rehospitalisation (n=NR) =€44,528 Hospitalisation costs per patient: • Rehospitalisation: €9445 • No rehospitalisation: €7796 Hardware costs = mean €18,741 per patient Total treatment costs (47-month period) = €761,043 (€28,186 per case)

Summary of model and comparators	Patient population	Unit costs	Patient outcomes	Total costs
Thavaneswaran (2016); United Kingdom				
Cost analysis to estimate reduction in medication costs in patients with occipital nerve stimulation (ONS) compared with usual care.	Patients with medically-intractable chronic cluster headache.	Resource use based on a 2011 German study; UK costs based on BNF and national tariff costs for 2015-16	Assumed a reduction in mean attack frequency (MAF) by at least 30% or 50% from ONS, assumed that this would translate to a proportional reduction in medication use	Main cost drivers are hospitalisations and acute medication. 30% reduction in headache frequency would reduce 1-year medication costs by approximately £1,200 50% reduction in headache frequency would reduce medication costs by approximately £1,400
Leone et al (2009); Italy				
Cost analysis to estimate direct costs associated with hypothalamic stimulation and medication cost savings after stimulation.	Patients with drug-resistant chronic cluster headache treated at one centre. N = 19 Mean Age = 42 years Male = 15	**Direct costs (2000 to 2008)** Cost of neurosurgery plus cost of Medtronic electrode = €25,000 Cost of follow up admissions = €2,000 per admission Cost of single sumatriptan injection = €25 Number of sumatriptan injections = 4 to 8 per day	Patients kept headache and medication use diary. Details NR. Assumed 4 to 8 attacks per day at baseline. Assumed 60% reduction in cluster headache frequency.	**Cumulative total costs for 19 patients (2008)** Implantations (electrodes plus surgery) = €475,000 Hospitalisations = €250,000 **Sumatriptan cost savings** = €3,573,125 **Total cost saving**s = €2,848,125

Abbreviations: CH, cluster headache; ED, emergency department; ONS, occipital nerve stimulation; NR, not reported; SPG, sphenopalatine ganglion stimulation; VNS, vagus nerve stimulation.

8.2.2 Quality assessment for each health economic study identified

We identified three economic evaluations of relevant interventions for cluster headache. These were all available as full-text publications and were all cost-utility models. All three were of high quality. The quality scores of these three publications are shown below in Table C8, based on the Drummond criteria.

Table C8: Quality assessment of relevant cost-effectiveness studies

Item/Study	(Morris et al. 2016)	(Mwamburi et al. 2017)	(Pietzsch et al. 2015)
1. The research question is stated.	Yes	Yes	Yes
2. The economic importance of the research question is stated.	Yes	Yes	Yes
3. The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes
4. The rationale for choosing alternative programmes or interventions compared is stated.	Yes	Yes	Yes
5. The alternatives being compared are clearly described.	Yes	Yes	Yes
6. The form of economic evaluation used is stated.	Yes	Yes	Yes
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	Yes
Data collection			
8. The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes
9. Details of the design and results of effectiveness study are given (if based on a single study).	Yes	Yes	Yes
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	NA (based on a single RCT)	No	NA (based on a single RCT)
11. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes
12. Methods to value benefits are stated.	Yes	Yes	Yes
13. Details of the subjects from whom valuations were obtained were given.	Yes	Yes	Yes
14. Productivity changes (if included) are reported separately.	NA	NA	NA
15. The relevance of productivity changes to the study question is discussed.	NA	NA	NA
16. Quantities of resource use are reported separately from their unit costs.	Yes	Yes	Yes
17. Methods for the estimation of quantities and unit costs are described.	Yes	Yes	Yes
18. Currency and price data are recorded.	Partly (cost year NR)	Yes	Yes
19. Details of currency of price adjustments for inflation or currency conversion are given.	No	Yes	Yes
20. Details of any model used are given.	Yes	Yes	Yes
21. The choice of model used and the key parameters on which it is based are justified.	Yes	Yes	Yes
Analysis and interpretation of results			
22. Time horizon of costs and benefits is stated.	Yes	Yes	Yes
23. The discount rate(s) is stated.	NA (1-year time horizon)	NA (1-year time horizon)	Yes

Item/Study	(Morris et al. 2016)	(Mwamburi et al. 2017)	(Pietzsch et al. 2015)
24. The choice of discount rate(s) is justified.	NA	NA	Yes
25. An explanation is given if costs and benefits are not discounted.	NA	NA	NA
26. Details of statistical tests and confidence intervals are given for stochastic data.	Partly	Partly	Partly
27. The approach to sensitivity analysis is given.	Yes	Yes	Yes
28. The choice of variables for sensitivity analysis is justified.	Yes	Yes	Yes
29. The ranges over which the variables are varied are justified.	Partly	Yes	Yes
30. Relevant alternatives are compared.	Yes	Yes	Yes
31. Incremental analysis is reported.	Yes	Yes	Yes
32. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Yes	Yes
33. The answer to the study question is given.	Yes	Yes	Yes
34. Conclusions follow from the data reported.	Yes	Yes	Yes
35. Conclusions are accompanied by the appropriate caveats	Yes	Yes	Yes

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

Abbreviations: NA, not applicable; NR, not reported; RCT, randomised controlled trial.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.
The de novo cost analysis developed should be relevant to the scope.
All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.
Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Rationale for undertaking further cost analysis in relation to the scope

As summarised in section 7.9.1, preventative use of gammaCore added to patients' existing standard of care (SoC) therapies, significantly reduced attack frequency compared with SoC alone in multiple studies, including a randomised controlled study in chronic cluster headache (cCH).

Significant efficacy of gammaCore for acute pain relief was demonstrated for patients with episodic cluster headache (eCH) in sham-controlled trials, with additional abortive benefits on attack severity and duration seen across studies. Reduction in attack frequency was reflected in a reduced use of abortive medication (high-flow oxygen and triptans) in the PREVA study and a real-world observational study conducted in the UK (Marin et al. 2018), hereafter referred to as the "Marin study".

If used, gammaCore is most likely to be introduced before more invasive procedures or treatment with lithium are considered (NICE. 2018a). The rationale for undertaking a *de novo* cost analysis is to demonstrate that use of gammaCore in CH alongside standard of care reduces use of abortive medication to a level that offsets any acquisition and ongoing costs of gammaCore, translating to cost savings to the NHS.

9.1.2 Patient group(s) included in the cost analysis

The *de novo* cost analysis considers the use of gammaCore in people over the age of 18 with cluster headache for whom preventive standard of care is ineffective or contraindicated. The model is designed to demonstrate cost offsets in patients who are using gammaCore for the prevention of chronic cluster headache.

The company acknowledges that the scope includes the acute use of gammaCore for cCH. Based on the ACT1 and ACT2 trials, there is insufficient evidence to support gammaCore as monotherapy when used acutely in cCH. In the Marin UK observational study, all of the cCH patients who used gammaCore acutely did so *in addition to* using it preventatively. As the gammaCore device will be supplied with sufficient doses to permit acute use *on top of* preventative doses per 3-month period (up to 30 doses/day), there would be no additional costs incurred by the NHS for acute use by patients already using gammaCore preventatively, and any further reduction in abortive medication use would be an upside not captured in the model.

The NICE scope also includes treatment of eCH, which is relevant to acute treatment only. Clinical data for eCH are available from ACT1 and ACT2 trials and from (Marin et al. 2018) (one patient only)**.** The ACT1 and ACT2 studies demonstrated higher nVNS treatment effects in eCH than in cCH, with an interaction test in ACT2 indicating a differential treatment effect between the eCH and cCH subgroups (*P*=0.04; type 3 test of fixed effects). However, the studies were not individually powered to detect any differential effects between the 2 subtypes (see section 7.6 and section 7.8.1). Given the lack of data to build an economic case in episodic use, and the small numbers of eCH patients likely to be offered gammaCore in the UK (1 out of 30 patients in the UK Marin study), eCH has not been considered in the cost analysis.

Technology and comparator

9.1.3 Justification if the comparator used in the cost analysis is different from the scope

The NICE scope includes the following comparators:

- Subcutaneous or nasal spray triptan therapy (acute)
- Oxygen therapy (at home), used alone or alongside subcutaneous or nasal spray triptan therapy (acute)
- Verapamil (preventative)
- Sphenopalatine ganglion nerve stimulators (acute and preventative treatment for chronic cluster headache)
- Occipital nerve block (preventative)

If used, gammaCore is most likely to be introduced before more invasive procedures or treatment with lithium are considered. The cost comparison model is in the cCH setting and compares the use of gammaCore plus SoC abortive medicine (subcutaneous or nasal spray triptan therapy and/or oxygen) vs. SoC abortive medicine alone. The model captures the reduced use of abortive therapy when gammaCore is used preventatively.

The cost comparison does not consider verapamil in preventative use, as there is insufficient evidence to support modelling reduced use of verapamil in patients who use gammaCore in either the preventative or acute setting. Patients in the PREVA trial were not permitted to reduce SoC prophylactic medicine use and only 8 of 30 patients recruited in the Marin UK observational study were taking verapamil, of which 2 discontinued use (Marin et al. 2018). Prophylactic medicines are therefore not included in the cost analysis as equal use of these in both arms would cancel out. This is a conservative assumption given that there is some indication of reduced use from the Marin study.

According to the 2015 NICE interventional procedures guidance (NICE. 2015), evidence for short-term efficacy of sphenopalatine ganglion nerve stimulators (acute and preventative treatment for cCH) was “adequate”. However, with regard to safety, the guidance states that “a variety of complications have been documented, most of which occur early and resolve; surgical revision of the implanted system is sometimes needed. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”

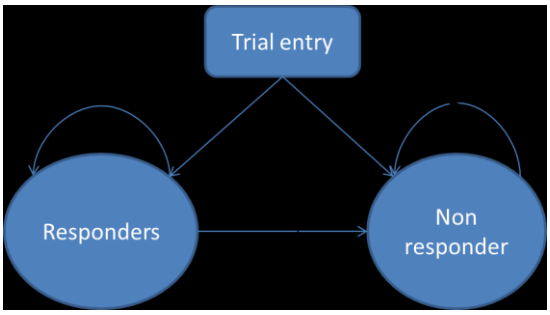
In November 2018, a clinical commissioning policy document was published by NHS England regarding use of sphenopalatine ganglion nerve stimulators in refractory cCH (NHS England. 2018). The conclusion of this document was that “there is not enough evidence to consider making the treatment available at this time.” As summarised in section 8.2.1, no UK cost analyses have been identified for sphenopalatine ganglion nerve stimulators. As this comparator is unlikely to be routinely used within the NHS in England, it is not included as a comparator in the cost analysis.

According to the 2012 NICE clinical guideline (NICE 2012), occipital nerve block is used as an option during pregnancy in order to permit discontinuation of verapamil. No later UK guidelines for use of occipital nerve block in refractory CH have been identified and frequency of use for the management of refractory CH is unknown. In the UK Marin study, one patient had bilateral implanted occipital nerve stimulation, but there were none described as having received occipital nerve block. As summarised in section 8.2.1, no UK cost analyses have been identified for occipital nerve block. As this comparator is unlikely to be routinely used within the NHS in England, it is not included as a comparator in the cost analysis.

Model structure

9.1.4 Diagram of the model structure chosen

Figure C2: Pharmacoeconomic model structure



In the base case, response was defined as a ≥50 % reduction from baseline in the number of CH attacks during the randomised period. Probability of response was modelled for the base case (response maintained) and for the following alternative scenarios: 1) constant rate of response loss, 2) diminishing rate of response loss, and 3) no initial response in the SoC group. Abbreviations: CH, cluster headache; SoC, standard of care.

9.1.5 Justification of the chosen structure in line with the clinical pathway of care identified in section 3.3

The population for consideration in the scope is people over the age of 18 with cluster headache for whom standard of care is ineffective or contraindicated. When standard of care fails, invasive treatments such as surgically implanted vagus nerve stimulators, deep brain stimulators (which require neurosurgery), occipital nerve stimulators, and sphenopalatine ganglion stimulators (NICE. 2015) may be considered. As explained in section 9.1.3, the only comparator in the scope that is used commonly in the NHS is SoC acute abortive medication.

The UK Marin study provides a precedent for use of gammaCore in the NHS that is generalisable to the pathway of care should gammaCore be recommended for use by NICE. In the Marin study, patients with CH who previously had an inadequate response and/or intolerable side effects with ≥3 current or previous CH treatments were offered gammaCore for use during a minimum evaluation period of 3 months. Physicians instructed patients to use gammaCore as preventive therapy, acute treatment, or both during this

period. Initial gammaCore dosing was based on established paradigms and titrated as necessary to achieve maximum benefit. Patients who reported a clinically meaningful decrease in the frequency, severity, or duration of their CH attacks after the evaluation period (i.e. patients considered as ‘responders’), were considered for inclusion in the individual funding request (IFR) process.

Should gammaCore be recommended for use in the NHS, the initial evaluation period would be tightly defined as 3 months, in line with the initial 93 days of free therapy supplied. Each refill card would only be dispensed once a refill order form is received from the patient’s specialist prescriber, thus ongoing costs of gammaCore would likely be contingent on a rolling assessment of response approximately every 3 months. The model captures this pathway by modelling a patient who has failed or is intolerant to SoC trialling gammaCore therapy preventatively, with optional acute ‘on top’ use. Patients do not change their use of preventative medication in the model and therefore preventative medicine is not captured explicitly in the model.

After an initial evaluation period of 3 months, during which patients are stratified into responders and non-responders, only those patients who are responders remain on gammaCore. These responders experience less frequent attacks and have reduced consumption of abortive medication while continuing to use gammaCore. As a gammaCore refill would be dispensed approximately every 3 months, subject to clinical assessment of response, costs of gammaCore are thereafter incurred in 3-month blocks, in patients who are responders at the start of the 3-month period only. Over each 3-month refill period, if any responders lose response, they revert to the non-responder health state but continue to incur gammaCore costs until the start of the next 3-month period, at which point they receive an assessment of response by the prescribing clinician and discontinue gammaCore.

In the PREVA trial, on which the cost analysis base case is modelled, a responder was defined as a patient with a ≥50 % reduction from baseline in the number of CH attacks per week. In order to explore this definition, which may differ in practice from that in PREVA, more and less stringent definitions

of responder were also considered in sensitivity analyses. Loss of response to gammaCore over time was also explored in sensitivity analyses.

9.1.6 List of all assumptions in the cost model and a justification for each assumption

- In the base case, treatment response is defined as ≥50% reduction from baseline in the number of CH attacks per week.
- Response rates to gammaCore in PREVA are generalisable to those of patients eligible for gammaCore in the NHS
- Beyond 1 month, responders in the SoC group are assumed to be non-responders.
- Non-responders in the gammaCore plus SoC group are assumed to discontinue prophylactic treatment with gammaCore after the 3-month evaluation period but continue use of abortive treatments.
- Patients are reassessed every 3 months for ongoing response and non-responders in the gammaCore plus SoC group discontinue prophylactic treatment with gammaCore. Discontinuation occurs in 3-month blocks in line with prescriptions for a gammaCore refill.
- use of abortive medication conditional on responder status is assumed to remain constant

9.1.7 Definition of what the model's health states are intended to capture

The model captures two health states, responder and non-responder. The responder health state represents the patients who achieve a defined minimum percentage reduction in attack frequency from baseline, ≥50% in the base case. The non-responder health state represents the patients who did not achieve the defined minimum percentage reduction in attack frequency from baseline. Abortive medication use (intranasal zolmitriptan, subcutaneous sumatriptan, and inhaled oxygen) is captured in both health states, with use

being lower in the responder health state. Use of gammaCore (in the gammaCore plus SoC arm only) is captured in both health states during the 3-month evaluation period. After 3-months, non-responders discontinue treatment in 3-month blocks, therefore each 3-month period includes a small number of patients who have lost response since the last assessment, and continue to use gammaCore until they are assessed for response at the start of the next 3-month prescription period, at which point they discontinue.

Loss of response following initial response to gammaCore is explored in sensitivity analyses, with treatment discontinuation in non-responders at 3-monthly assessments. In the base case analysis, subjects from the gammaCore plus SoC group who were responders throughout the extension phase of PREVA were assumed to maintain this response until the end of the model time horizon (1 year).

9.1.8 Key features of the cost model not previously reported

Table C9: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	1 year	PREVA trial was of only 8 weeks duration. A 1-year horizon preserves robustness and avoids introducing unnecessary uncertainty.	
Discount of 3.5% for costs	3.5%	In line with reference case.	
Perspective (NHS/PSS)	NHS	PSS costs are not relevant to the analysis.	
Cycle length	1 month	Sufficient to capture changes in response status and abortive medication use.	

Abbreviations: NHS, National Health Service; PSS, Personal Social Services.

9.2 Clinical parameters and variables

9.2.1 Description of how the data from the clinical evidence were used in the cost analysis

Model parameter estimates were derived from data on the reduction in attack frequency and the use of abortive medications from the randomised and extension phases of PREVA (see section 7.4.1 and section 7.4.6). In the base case, treatment response was defined as ≥50 % reduction from baseline in the number of CH attacks per week, by comparing matched data of attack frequency during the run-in and randomised phases of PREVA. The probability of being a responder was calculated on an ITT basis, with patients not providing matched attack frequency data imputed as non-responders.

A post-hoc analysis of abortive medication use from the last 14 days of the PREVA randomised phase was used to assess health care resource utilisation in the gammaCore arm, conditional on responder status. As not all patients with matched responder data had matched abortive medication data available, the abortive medication use was obtained from a subset of the patients who provided response data. Abortive medication use (triptans and oxygen) in the gammaCore arm was extracted from matched patient data stratified into responders and non-responders according to whether they achieved a minimum reduction in attack frequency (≥50% in the base case) during the randomised phase.

In the gammaCore arm, medication use in patients identified as responders was used to inform abortive medication use in the responder health state. During the first 3 months of treatment, the evaluation period during which both responder and non-responders are using gammaCore, medication use for non-responders was obtained from patients identified as non-responders from the randomised phase of PREVA (matched data only). After the initial 3 months, non-responders were assumed to discontinue gammaCore and revert to the level of medication use in the SoC arm of the PREVA trial. In a sensitivity analysis, after the initial 3 months, non-responders were assumed

to revert back to their medication use observed at baseline (collected during the run-in period of PREVA).

In the SoC arm, the probability of being a responder in the first month was assumed to be as reported in the ITT analysis of the PREVA trial (based on a ≥50% reduction in attack frequency). Responders in the SoC arm were assumed to revert to non-responder status after the first month. Conservatively, medication use in the responder state of the SoC arm was assumed to be the same as the medication use for responders in the gammaCore arm (for the 50% responder definition only, as only one response definition is relevant and necessary for the SoC arm). Medication use in the non-responder health state of the SoC arm was the mean use in the SoC arm of PREVA reported during the randomised phase (Gaul et al. 2016).

A further sensitivity analysis was conducted assuming that no patients in the SoC arm were responders in the first month (i.e. medication use was the mean reported in the SoC arm during the randomised period of PREVA for all cycles).

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The PREVA trial was of 8 weeks duration (4 weeks for the randomised period). Therefore, the model required extrapolation beyond that time point. The main source of uncertainty is maintenance of response over time and use of abortive medication conditional on responder status (i.e. attack frequency).

Response loss scenarios were explored by fitting an exponential survival curve function to data from patients in the nVNS and SoC group on the basis of their response statuses at the end of the randomised phase and at the end of the extension phase. The exponential curve was fitted according to the base case response definition of ≥50% reduction in attack frequency. The same curve was applied to all the response definition scenarios for simplicity.

In the base case analysis, subjects from the gammaCore plus SoC group who were responders throughout the extension phase of PREVA were assumed to maintain this response until the end of the model time horizon (1 year). Thus there is an initial loss of response after 1 month of treatment as reflected in the PREVA trial, but after the 2nd month patients retain their response.

Resource use in the gammaCore plus SoC group, *conditional on response status*, was assumed to remain the same from the randomised phase to the end of the 1-year time horizon. Resource use in the SoC only group was assumed to remain the same from the randomised phase to the end of the 1-year time horizon. In the post-hoc analysis of medication use by responder status, use neither consistently increased nor decreased between the randomised and extension phases of PREVA in patients with matched data.

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Not applicable.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events (AEs) as reported in section 7.7 were generally benign, with no AEs requiring hospitalisation. In the UK Marin study, no serious device-related AEs were reported during gammaCore therapy. Observed AEs in this patient cohort included redness and muscle soreness at the stimulation site, which were also reported in previous randomised clinical trials. Consistent with these previous studies, AEs were mild and transient and were typically reported early in the evaluation period, when the use of gammaCore was relatively novel. It is anticipated that reported AEs would be largely self-

managed and would not incur any NHS costs. Therefore, no costs related to AEs were included in the model.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

Not applicable.

9.2.6 Summary of all the variables included in the cost analysis

Table C10: Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)			Source
Probability of response (≥50% reduction) - SoC	8.3%	2.4%	17.5%	Beta	Gaul et al., 2016
Probability of response – gCore (≥25% reduction)	60%	45%	74%	Beta	Post hoc analysis of PREVA (ITT basis)
Probability of response – gCore (≥40% reduction)	47%	32%	61%	Beta	Post hoc analysis of PREVA (ITT basis)
Probability of response – gCore (≥50% reduction)	40.0%	26.3%	54.5%	Beta	Gaul et al., 2016 (ITT basis)
Probability of response – gCore (≥65% reduction)	24%	13%	38%	Beta	Post hoc analysis of PREVA (ITT basis)
Probability of response – gCore (≥50% reduction, using means from each arm)	40.0%	26.3%	54.5%	Beta	Post hoc analysis of PREVA (ITT basis)
Probability of discontinued response per month for initial responders	31.0%	16.2%	54.1%	Normal	Post hoc analysis of PREVA (ITT basis)
zolmitriptan doses per 14 days - SoC responder	0.60	0.10	1.52	Gamma	Assumed to be same as a gammaCore responder at 50% response definition, Gaul et al., 2016
sumatriptan doses per 14 days - SoC responder	2.50	1.04	4.59	Gamma	Assumed to be same as a gammaCore responder at 50% response definition, Gaul et al., 2016
oxygen doses per 14 days - SoC responder	2.20	0.56	4.94	Gamma	Assumed to be same as a gammaCore responder at 50% response definition, Gaul et al., 2016
zolmitriptan doses per 14 days - SoC non responder	1.30	0.45	2.59	Gamma	SoC arm, Gaul et al., 2016
sumatriptan doses per 14 days - SoC non responder	7.50	4.88	10.67	Gamma	SoC arm, Gaul et al., 2017
oxygen doses per 14 days - SoC non responder	10.80	6.68	15.90	Gamma	SoC arm, Gaul et al., 2018
≥25% reduction response definition					
zolmitriptan doses per 14 days - gCore responder	0.80	0.23	1.73	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore responder	2.50	1.27	4.14	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore responder	3.50	1.79	5.78	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (on Tx)	3.80	0.17	12.82	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (on Tx)	5.80	0.65	16.47	Gamma	Post hoc analysis of PREVA

Variable	Value	Range or 95% CI (distribution)			Source
oxygen doses per 14 days - gCore non responder (on Tx)	16.20	6.11	31.12	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (baseline)	4.80	0.13	17.63	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (baseline)	3.80	0.75	9.28	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (baseline)	16.30	5.84	32.03	Gamma	Post hoc analysis of PREVA
≥40% reduction response definition					
zolmitriptan doses per 14 days - gCore responder	1.00	0.28	2.16	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore responder	3.00	1.48	5.06	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore responder	2.80	1.06	5.36	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	0.17	7.83	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.70	0.48	10.14	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (on Tx)	12.20	5.53	21.46	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.30	0.18	10.83	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (baseline)	2.90	0.84	6.22	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (baseline)	19.30	8.50	34.46	Gamma	Post hoc analysis of PREVA
≥50% reduction response definition					
zolmitriptan doses per 14 days - gCore responder	0.60	0.10	1.52	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore responder	2.50	1.04	4.59	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore responder	2.20	0.56	4.94	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	0.32	6.89	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (on Tx)	4.10	1.00	9.33	Gamma	Post hoc analysis of PREVA

Variable	Value	Range or 95% CI (distribution)			Source
oxygen doses per 14 days - gCore non responder (on Tx)	11.20	5.45	18.98	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	0.55	10.13	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (baseline)	4.50	2.07	7.85	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (baseline)	18.60	9.35	30.98	Gamma	Post hoc analysis of PREVA
≥65% reduction response definition					
zolmitriptan doses per 14 days - gCore responder	0.00	0.00	0.00	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore responder	2.00	0.77	3.81	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore responder	0.70	0.10	1.88	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.20	0.46	5.29	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.80	1.29	7.64	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (on Tx)	9.20	4.76	15.09	Gamma	Post hoc analysis of PREVA
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	1.06	8.26	Gamma	Post hoc analysis of PREVA
sumatriptan doses per 14 days - gCore non responder (baseline)	5.00	2.71	7.97	Gamma	Post hoc analysis of PREVA
oxygen doses per 14 days - gCore non responder (baseline)	31.00	9.68	64.51	Gamma	Post hoc analysis of PREVA
≥50% reduction response definition (using means from each arm)					
zolmitriptan doses per 14 days - gCore responder	1.60	0.29	3.99	Gamma	Gaul et al., 2016
sumatriptan doses per 14 days - gCore responder	2.80	1.59	4.35	Gamma	Gaul et al., 2016
oxygen doses per 14 days - gCore responder	6.50	3.27	10.83	Gamma	Gaul et al., 2016
zolmitriptan doses per 14 days - gCore non responder (on Tx)	1.30	0.45	2.59	Gamma	Gaul et al., 2016
sumatriptan doses per 14 days - gCore non responder (on Tx)	7.50	4.88	10.67	Gamma	Gaul et al., 2016

Variable	Value	Range or 95% CI (distribution)			Source
oxygen doses per 14 days - gCore non responder (on Tx)	10.80	6.68	15.90	Gamma	Gaul et al., 2016
zolmitriptan doses per 14 days - gCore non responder (baseline)	1.30	0.45	2.59	Gamma	Gaul et al., 2016
sumatriptan doses per 14 days - gCore non responder (baseline)	7.50	4.88	10.67	Gamma	Gaul et al., 2016
oxygen doses per 14 days - gCore non responder (baseline)	10.80	6.68	15.90	Gamma	Gaul et al., 2016
% of oxygen treatments that are portable	50.0%	0.0%	60.0%	Beta	Assumption
% of sumatriptan treatments that are s.c.	86.7%	66.1%	98.2%	Beta	Marin et al 2018
zolmitriptan nasal per unit cost	£6.08			Fixed	zolmitriptan 5mg/0.1ml nasal spray, NHS drug tariff March 2019
sumatriptan s.c. per unit cost	£19.75			Fixed	sumatriptan 6mg/0.5ml subcutaneous injection, NHS drug tariff March 2019
sumatriptan nasal per unit cost	£7.08			Fixed	sumatriptan 10mg/0.1ml nasal spray, NHS drug tariff March 2019
oxygen per unit cost - static	£0.56	0.50	0.63	Gamma	Calculated using East of England Priorities Advisory Committee, 2017 and baseline oxygen use in PREVA trial
oxygen per unit cost - portable	£0.79	0.70	0.88	Gamma	Calculated using East of England Priorities Advisory Committee, 2017 and baseline oxygen use in PREVA trial
gCore first 3 months cost	£0.00			Fixed	First 3 months free, electroCore
gCore cost per 3 months	£625.00			Fixed	electroCore

Abbreviations: CI, confidence interval; gCore, gammaCore; Tx, treatment; s.c., subcutaneous.

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Description of how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff

The comparator in the cost analysis is SoC abortive medication use alone, which is prescribed by specialist neurologists in secondary and tertiary care centres. gammaCore would also be prescribed via this route and training would be provided free by electroCore. Clinical reviews to provide 3-monthly prescriptions of gammaCore would be as per current patient follow-up for SoC medication. The clinical pathway would therefore not change and no change in NHS resource other than SoC abortive medicine use is anticipated. Abortive medicine use is sourced directly from the PREVA trial.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition

gammaCore is non-invasive and would be used in addition to SoC abortive medication, therefore OPCS codes are not relevant. Invasive procedures such as occipital nerve block or sphenopalatine ganglion stimulation would be used after gammaCore in the treatment pathway.

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

This was not carried out as the only change in resource relevant to the cost analysis is the use of abortive medication, which is sourced from the PREVA trial.

The cost of a unit of oxygen is uncertain due to the many suppliers and the quantity used per dose, and as summarised in section 8.2.1, there is a paucity of costing studies available for oxygen. The cost of oxygen treatment was estimated using information from a document informing local NHS commissioning in cluster headache (East of England priorities advisory committee. 2017). Treatments are assumed to last 20 minutes and consume 240 to 300L of oxygen per treatment assuming a 12-15L/min flow rate. A patient with episodic cluster headache is assumed to have 5 ZH 2,400L static cylinders requiring refilling 4 times per year (48,000L in total), at a cost per year for the oxygen refills of £100. Portable oxygen refills, which are smaller and more frequent, are assumed to cost 40% more. A cost/L of oxygen was calculated using this information, ranging from £2.08 to £2.92 per 1000L.

In the PREVA trial, patients at baseline used 14.6 oxygen treatments over 2 weeks. Using the standard error of 2.27 for number of treatments and the assumption of 240-300L per treatment led to consumption estimates of 65,515 to 151,057L per cCH patient per year. Considering together the lower to upper estimates of cost/1,000L and the lower and upper estimates of litres of oxygen consumed led to unit cost estimates of 50-63p per treatment for static supplies and 70-88p per treatment for portable supplies.

Validity of the cost of oxygen per treatment was tested by estimating annual oxygen use costs based on the PREVA oxygen use at baseline and comparing this with 2016/17 costs obtained from NHS clinical commissioning groups (CCGs) via a freedom of information (FOI) request. Assuming that 50% of treatments use portable oxygen, the estimated unit costs predicted a

mean of £271 of oxygen costs per patient per year (range £164-£378) vs. average costs provided by the CCGs of £274 (range £198 to £347). Note that the CCG costs included those from episodic patients. The costs include only provision of oxygen refills and not rental or assessment fees which remain constant regardless of the amount of oxygen consumed.

In the PREVA trial only subcutaneous sumatriptan was used whereas two patients in the Marin study used nasal sumatriptan. In order to make the model more generalisable to UK patients a proportion of the patients (2 out of 15 sumatriptan patients; 13%) were assumed to use nasal sumatriptan.

9.3.4 Details of the process used when clinical advisers assessed the applicability of the resources used in the model[1]

Not applicable.

Technology and comparators' costs

9.3.5 List price for the technology

The gammaCore device, conductive gel consumables, and first 93-day activation card are currently provided free of charge to the NHS. This allows the effectiveness of the treatment in individual users to be assessed before further treatment is bought. If the trial is successful, further treatment (through new activation cards) costs £625 for 93 days of use (exclusive of VAT).

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

As above.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

9.3.7 Summary of the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model

Table C11: Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£625 for 93 days of use (exclusive of VAT) after the first 3 months.	electroCore

Costs per treatment/patient associated with the comparator technology in the cost model

Not applicable as the comparator is not another technology.

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Health state costs vary according to the selected definition of a responder, as they are the product of the abortive medication use in the responder and non-responder health states and the unit cost of the abortive medication.

As the definition of a gammaCore responder is varied in the model, the costs of a gammaCore non-responder will also vary, because during the 3-month evaluation period, non-responders include patients who have responded to gammaCore, but not at the threshold defined by the response definition. Abortive medication consumption by responder definition has already been described in Table C11, therefore only the values for a responder definition of ≥50% reduction in attack frequency are presented in Table C12.

Note that the cost of gammaCore is not included in these health state costs. While the cost of gammaCore in responders remains constant (£208.33 per

patient per month), the cost in non-responders varies according to whether any patients have lost response since the last response assessment.

Table C12: List of health states and associated costs in the economic model

Health states	Items	Value	Reference
Responder (≥50% reduction in attack frequency definition)	*Sumatriptan*	£106.98	Product of 1 month of doses and unit cost
	Zolmitriptan	£7.91	
	Oxygen	£3.22	
	Total	**£118.11**	
Non-Responder	*Sumatriptan*	£320.94	Product of 1 month of doses and unit cost
	Zolmitriptan	£17.13	
	Oxygen	£15.80	
	Total	**£353.87**	
Non-Responder (while on treatment, gCore 1st 3 months only)	*Sumatriptan*	£175.45	Product of 1 month of doses and unit cost
	Zolmitriptan	£32.95	
	Oxygen	£16.38	
	Total	**£224.78**	

Abbreviation: gCore, gammaCore.

Adverse-event costs

9.3.9 Details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model, including all adverse events and complication costs, both during and after longer-term use of the technology

Not applicable; no events considered in section 9.2.4.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The present analysis was conservative in that it included only the costs associated with use of abortive medications without accounting for other potential sources of cost savings (e.g. reduced preventative medication,

reduced frequency of clinic visits, fewer hospitalisations due to adverse events of abortive medication and verapamil). These were not captured during the PREVA and other trials reported in section 7.6 or section 7.7.3, which were of short duration. The Marin study did not report any hospitalisations.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

The base case analysis defines treatment response as a ≥50% reduction in attack frequency vs baseline, according to the PREVA trial definition. However, in the UK Marin study, submission for an IFR was discouraged for patients who did not achieve a ≥ 25% decrease in weekly attack frequency, suggesting that the threshold for what is considered a clinically meaningful response may be lower. The % reduction in weekly attack frequency observed in patients who obtained funding in the Marin study was 64% (9.5 [0–38.5] vs. 26.6 [3.8–77.0] at baseline). In order to explore alternative definitions of responder, the model considers responder definitions of ≥40%, ≥25%, ≥50%, and ≥65% reduction in attack frequency or more from baseline (additional definitions of ≥30% and ≥60% were explored, but the results were identical to those for ≥25% and ≥65% reduction, respectively). A further ≥50% reduction

in attack frequency scenario was explored which followed the methods used by Morris et al., 2016, whereby mean medication use in the nVNS plus SoC arm during the randomised phase of PREVA informed the responder health states and mean medication use in the SoC arm during the randomised phase of PREVA informed the non-responder health state.

The base case applies the medication data from the randomised phase of the SoC arm of PREVA to the gammaCore non-responder health states who have discontinued gammaCore (i.e. following the 3-month evaluation period). Alternative scenarios were explored where the baseline medication use for gammaCore non-responders was applied to the non-responder health states who had discontinued gammaCore. This was done to capture any potential differences in medication use at baseline between responders and non-responders.

The base case analysis assumes an initial loss of response as observed between the randomised and extension phases of PREVA, leading to a single reduction in response after the first 1-month cycle. The rate of this initial loss of response was estimated by fitting an exponential survival curve function to data from patients in the nVNS plus SoC group of the PREVA trial on the basis of their response statuses at the end of the randomised phase and at the end of the extension phase. In the base case, no loss of response to gammaCore after 2 months of treatment (the end of the extension phase of the PREVA trial) was assumed. Two alternative scenarios were explored regarding loss of response (and subsequent discontinuation of gammaCore). In the first alternative scenario, the exponential function was used to predict patient response status beyond 1 month (i.e. beyond the randomised phase) assuming a constant monthly rate (~31 %) of response loss throughout the course of the model. The second scenario was modelled assuming a diminishing rate of response loss; that is, the rate at which response was lost beyond 1 month (as predicted by the exponential function) was reduced by a fixed percentage (10%) each month.

The above scenarios were modelled in alternative combinations using multi-way scenario analysis.

A further scenario was also modelled in which no patients in the SoC-alone group were assumed to have responded initially, and all other assumptions were the same as in the base case. As this had little effect on the cost estimates, it was carried out as a single scenario keeping other assumptions constant.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

One-way sensitivity analysis (OWSA) was carried out on any variables with uncertainty estimates. These comprised primarily the probability of response and use of abortive medication conditional on response from the PREVA study. The cost of a unit of oxygen is uncertain due to the many suppliers and the quantity used per dose. Therefore, this was also included in the OWSA, varying the cost between the highest and lowest estimates of unit cost.

Probabilistic sensitivity analysis (PSA) was undertaken using a Markov chain Monte Carlo simulation. Distributions for each model parameter of interest were estimated in line with best practice. A probabilistic analysis with 1000 simulations for each scenario was conducted, and mean values from this analysis were calculated.

9.4.3 Summary of the variables used in the sensitivity analysis

Table C13: Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values	
Probability of response (≥50% reduction) - SoC	8.3%	2.4%	17.5%
Probability of response – gCore (≥25% reduction)	60%	45%	74%
Probability of response – gCore (≥40% reduction)	47%	32%	61%
Probability of response – gCore (≥50% reduction)	40%	26%	55%
Probability of response – gCore (≥65% reduction)	24%	13%	38%
Probability of response – gCore (≥50% reduction, using means from each arm)	40%	26%	55%
Probability of discontinued response per month for initial responders	31.0%	16.2%	54.1%
zolmitriptan doses per 14 days - SoC responder	0.60	0.10	1.52
sumatriptan doses per 14 days - SoC responder	2.50	1.04	4.59
oxygen doses per 14 days - SoC responder	2.20	0.56	4.94
zolmitriptan doses per 14 days - SoC non responder	1.30	0.45	2.59
sumatriptan doses per 14 days - SoC non responder	7.50	4.88	10.67
oxygen doses per 14 days - SoC non responder	10.80	6.68	15.90
≥25% reduction response definition			
zolmitriptan doses per 14 days - gCore responder	0.80	0.23	1.73
sumatriptan doses per 14 days - gCore responder	2.50	1.27	4.14
oxygen doses per 14 days - gCore responder	3.50	1.79	5.78
zolmitriptan doses per 14 days - gCore non responder (on Tx)	3.80	0.17	12.82
sumatriptan doses per 14 days - gCore non responder (on Tx)	5.80	0.65	16.47
oxygen doses per 14 days - gCore non responder (on Tx)	16.20	6.11	31.12
zolmitriptan doses per 14 days - gCore non responder (baseline)	4.80	0.13	17.63
sumatriptan doses per 14 days - gCore non responder (baseline)	3.80	0.75	9.28
oxygen doses per 14 days - gCore non responder (baseline)	16.30	5.84	32.03
≥40% reduction response definition			
zolmitriptan doses per 14 days - gCore responder	1.00	0.28	2.16

Variable	Base-case value	Range of values	
sumatriptan doses per 14 days - gCore responder	3.00	1.48	5.06
oxygen doses per 14 days - gCore responder	2.80	1.06	5.36
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	0.17	7.83
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.70	0.48	10.14
oxygen doses per 14 days - gCore non responder (on Tx)	12.20	5.53	21.46
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.30	0.18	10.83
sumatriptan doses per 14 days - gCore non responder (baseline)	2.90	0.84	6.22
oxygen doses per 14 days - gCore non responder (baseline)	19.30	8.50	34.46
≥50% reduction response definition			
zolmitriptan doses per 14 days - gCore responder	0.60	0.10	1.52
sumatriptan doses per 14 days - gCore responder	2.50	1.04	4.59
oxygen doses per 14 days - gCore responder	2.20	0.56	4.94
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	0.32	6.89
sumatriptan doses per 14 days - gCore non responder (on Tx)	4.10	1.00	9.33
oxygen doses per 14 days - gCore non responder (on Tx)	11.20	5.45	18.98
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	0.55	10.13
sumatriptan doses per 14 days - gCore non responder (baseline)	4.50	2.07	7.85
oxygen doses per 14 days - gCore non responder (baseline)	18.60	9.35	30.98
≥65% reduction response definition			
zolmitriptan doses per 14 days - gCore responder	0.00	0.00	0.00
sumatriptan doses per 14 days - gCore responder	2.00	0.77	3.81
oxygen doses per 14 days - gCore responder	0.70	0.10	1.88
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.20	0.46	5.29
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.80	1.29	7.64
oxygen doses per 14 days - gCore non responder (on Tx)	9.20	4.76	15.09
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	1.06	8.26
sumatriptan doses per 14 days - gCore non responder (baseline)	5.00	2.71	7.97
oxygen doses per 14 days - gCore non responder (baseline)	31.00	9.68	64.51

Variable	Base-case value	Range of values	
≥50% reduction response definition (using means from each arm)			
zolmitriptan doses per 14 days - gCore responder	1.60	0.29	3.99
sumatriptan doses per 14 days - gCore responder	2.80	1.59	4.35
oxygen doses per 14 days - gCore responder	6.50	3.27	10.83
zolmitriptan doses per 14 days - gCore non responder (on Tx)	1.30	0.45	2.59
sumatriptan doses per 14 days - gCore non responder (on Tx)	7.50	4.88	10.67
oxygen doses per 14 days - gCore non responder (on Tx)	10.80	6.68	15.90
zolmitriptan doses per 14 days - gCore non responder (baseline)	1.30	0.45	2.59
sumatriptan doses per 14 days - gCore non responder (baseline)	7.50	4.88	10.67
oxygen doses per 14 days - gCore non responder (baseline)	10.80	6.68	15.90
% of oxygen treatments that are portable	50.0%	0.0%	60.0%
% of sumatriptan treatments that are s.c.	86.7%	66.1%	98.2%
oxygen per unit cost - static	£0.56	0.50	0.63
oxygen per unit cost - portable	£0.79	0.70	0.88

Abbreviations: CI, confidence interval; gCore, gammaCore; Tx, treatment; s.c., subcutaneous.

Table C14: Variables used in multi-way scenario-based sensitivity analysis

Responder definition	Response loss assumption	Non-responder use assumption
25%	No response loss post month 2	SoC non-responder use from PREVA
25%	No response loss post month 2	gammaCore non-responder use from PREVA
25%	Constant rate of response loss	SoC non-responder use from PREVA
25%	Constant rate of response loss	gammaCore non-responder use from PREVA
25%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
25%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
40%	No response loss post month 2	SoC non-responder use from PREVA

Responder definition	Response loss assumption	Non-responder use assumption
40%	No response loss post month 2	gammaCore non-responder use from PREVA
40%	Constant rate of response loss	SoC non-responder use from PREVA
40%	Constant rate of response loss	gammaCore non-responder use from PREVA
40%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
40%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
50% using means[1]	No response loss post month 2	SoC non-responder use from PREVA
50% using means[1]	No response loss post month 2	gammaCore non-responder use from PREVA
50% using means[1]	Constant rate of response loss	SoC non-responder use from PREVA
50% using means[1]	Constant rate of response loss	gammaCore non-responder use from PREVA
50% using means[1]	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
50% using means[1]	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
50%	No response loss post month 2	SoC non-responder use from PREVA
50%	No response loss post month 2	gammaCore non-responder use from PREVA
50%	Constant rate of response loss	SoC non-responder use from PREVA
50%	Constant rate of response loss	gammaCore non-responder use from PREVA
50%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
50%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA
65%	No response loss post month 2	SoC non-responder use from PREVA
65%	No response loss post month 2	gammaCore non-responder use from PREVA
65%	Constant rate of response loss	SoC non-responder use from PREVA
65%	Constant rate of response loss	gammaCore non-responder use from PREVA
65%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA
65%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA

1, Morris at al (2016) approach as described in section 9.4.1.

Table C15: Variable values used in probabilistic sensitivity analysis

Variable	Value	Distribution
Probability of response (≥50% reduction) - SoC	8.3%	Beta
Probability of response – gCore (≥25% reduction)	60%	Beta
Probability of response – gCore (≥40% reduction)	47%	Beta
Probability of response – gCore (≥50% reduction)	40%	Beta
Probability of response – gCore (≥65% reduction)	24%	Beta
Probability of response – gCore (≥50% reduction, using means from each arm)	40%	Beta
Probability of discontinued response per month for initial responders	31.0%	Normal (coefficient from exponential distribution)
zolmitriptan doses per 14 days - SoC responder	0.60	Gamma
sumatriptan doses per 14 days - SoC responder	2.50	Gamma
oxygen doses per 14 days - SoC responder	2.20	Gamma
zolmitriptan doses per 14 days - SoC non responder	1.30	Gamma
sumatriptan doses per 14 days - SoC non responder	7.50	Gamma
oxygen doses per 14 days - SoC non responder	10.80	Gamma
≥25% reduction response definition		
zolmitriptan doses per 14 days - gCore responder	0.80	Gamma
sumatriptan doses per 14 days - gCore responder	2.50	Gamma
oxygen doses per 14 days - gCore responder	3.50	Gamma
zolmitriptan doses per 14 days - gCore non responder (on Tx)	3.80	Gamma
sumatriptan doses per 14 days - gCore non responder (on Tx)	5.80	Gamma
oxygen doses per 14 days - gCore non responder (on Tx)	16.20	Gamma
zolmitriptan doses per 14 days - gCore non responder (baseline)	4.80	Gamma
sumatriptan doses per 14 days - gCore non responder (baseline)	3.80	Gamma
oxygen doses per 14 days - gCore non responder (baseline)	16.30	Gamma
≥40% reduction response definition		
zolmitriptan doses per 14 days - gCore responder	1.00	Gamma
sumatriptan doses per 14 days - gCore responder	3.00	Gamma

Variable	Value	Distribution
oxygen doses per 14 days - gCore responder	2.80	Gamma
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	Gamma
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.70	Gamma
oxygen doses per 14 days - gCore non responder (on Tx)	12.20	Gamma
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.30	Gamma
sumatriptan doses per 14 days - gCore non responder (baseline)	2.90	Gamma
oxygen doses per 14 days - gCore non responder (baseline)	19.30	Gamma
≥50% reduction response definition		
zolmitriptan doses per 14 days - gCore responder	0.60	Gamma
sumatriptan doses per 14 days - gCore responder	2.50	Gamma
oxygen doses per 14 days - gCore responder	2.20	Gamma
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	Gamma
sumatriptan doses per 14 days - gCore non responder (on Tx)	4.10	Gamma
oxygen doses per 14 days - gCore non responder (on Tx)	11.20	Gamma
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	Gamma
sumatriptan doses per 14 days - gCore non responder (baseline)	4.50	Gamma
oxygen doses per 14 days - gCore non responder (baseline)	18.60	Gamma
≥65% reduction response definition		
zolmitriptan doses per 14 days - gCore responder	0.00	Gamma
sumatriptan doses per 14 days - gCore responder	2.00	Gamma
oxygen doses per 14 days - gCore responder	0.70	Gamma
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.20	Gamma
sumatriptan doses per 14 days - gCore non responder (on Tx)	3.80	Gamma
oxygen doses per 14 days - gCore non responder (on Tx)	9.20	Gamma
zolmitriptan doses per 14 days - gCore non responder (baseline)	3.80	Gamma
sumatriptan doses per 14 days - gCore non responder (baseline)	5.00	Gamma
oxygen doses per 14 days - gCore non responder (baseline)	31.00	Gamma
zolmitriptan doses per 14 days - gCore responder	1.60	Gamma

Variable	Value	Distribution
sumatriptan doses per 14 days - gCore responder	2.80	Gamma
oxygen doses per 14 days - gCore responder	6.50	Gamma
zolmitriptan doses per 14 days - gCore non responder (on Tx)	1.30	Gamma
sumatriptan doses per 14 days - gCore non responder (on Tx)	7.50	Gamma
oxygen doses per 14 days - gCore non responder (on Tx)	10.80	Gamma
zolmitriptan doses per 14 days - gCore non responder (baseline)	1.30	Gamma
sumatriptan doses per 14 days - gCore non responder (baseline)	7.50	Gamma
oxygen doses per 14 days - gCore non responder (baseline)	10.80	Gamma
% of oxygen treatments that are portable	50.0%	Beta
% of sumatriptan treatments that are s.c.	86.7%	Beta
oxygen per unit cost - static	£0.56	Gamma
oxygen per unit cost - portable	£0.79	Gamma

Abbreviations: CI, confidence interval; gCore, gammaCore; Tx, treatment; s.c., subcutaneous.

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

Unit costs of triptans and the cost of gammaCore were omitted from the analysis as these are constant.

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- Costs
- Disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- A tabulation of the mean cost results
- Results of the sensitivity analysis.

Base-case analysis

9.5.1 Total costs associated with use of the technology and the comparator(s) in the base-case analysis

Table C16: Base-case results

	Total per patient cost (£)
gammaCore plus SoC	£3,448.45
SoC	£3,898.86
Difference	-£450.42

9.5.2 Total difference in costs between the technology and comparator(s)

Use of gammaCore resulted in £450.42 of cost savings over 1 year in the model.

9.5.3 Details of the costs for the technology and its comparator by category of cost

Table C17: Summary of costs by category of cost per patient

Item	***Cost gammaCore plus SoC***	***Cost SoC***	***Increment***
GC cost	*£517.18*		*£517.18*
Sumatriptan	*£2,577.39*	*£3,505.53*	*-£928.13*
Zolmitriptan	*£206.33*	*£204.85*	*£1.48*
Oxygen	*£147.55*	*£188.49*	*-£40.95*
Total	***£3,448.45***	***£3,898.86***	***-£450.42***

9.5.4 Details of the costs for the technology and its comparator by health state

Table C18: Summary of costs by health state per patient

Health state	***Cost gammaCore plus SoC***	***Cost SoC***	***Increment***
Responder	*£891.34*	*£9.08*	*£882.26*
Non-Responder	*£2,557.11*	*£3,889.79*	*-£1,332.68*
Total	***£3,448.45***	***£3,898.86***	***-£450.42***

9.5.5 Details of the costs for the technology and its comparator by adverse event, if appropriate

Not applicable.

Sensitivity analysis results

9.5.6 Results of deterministic one-way sensitivity analysis of the variables described in Table C13

Only the top 10 parameters with the greatest influence are shown, in descending order of impact, using the base case assumptions (≥50% response definition, no response loss after 2 months, abortive medication use from PREVA SoC arm for non-responders).

Table C19: Results of deterministic one-way sensitivity analysis

Parameter	Mean	Lower bound value	Upper bound value	Lower bound cost	Upper bound cost	Cost difference
Base case cost						***-£450.42***
sumatriptan doses per 14 days - SoC non responder	7.50	4.88	10.67	£103	-£1,120	£1,223
sumatriptan doses per 14 days - gCore non responder (on Tx)	4.10	1.00	9.33	-£699	-£31	£668
sumatriptan doses per 14 days - gCore responder	2.50	1.04	4.59	-£647	-£169	£477
% of sumatriptan treatments that are s.c.	0.87	0.66	0.98	-£317	-£526	£209
zolmitriptan doses per 14 days - gCore non responder (on Tx)	2.50	0.32	6.89	-£509	-£332	£178
zolmitriptan doses per 14 days - SoC non responder	1.30	0.45	2.59	-£390	-£542	£153
Probability of response - gCore	0.40	0.26	0.55	-£410	-£493	£84
oxygen doses per 14 days - SoC non responder	10.80	6.68	15.90	-£418	-£491	£73
zolmitriptan doses per 14 days - gCore responder	0.60	0.10	1.52	-£473	-£409	£64
Probability of discontinued response per month for initial responders	0.31	0.16	0.54	-£467	-£424	£43

Abbreviations: CI, confidence interval; gCore, gammaCore; Tx, treatment; s.c., subcutaneous.

9.5.7 Results of deterministic multi-way scenario sensitivity analysis described in Table C14

Table C20: Results of deterministic multi-way scenario sensitivity analysis

Responder definition	Response loss assumption	Non-responder use assumption	gammaCore plus SoC	SoC	Difference
25%	No response loss post month 2	SoC non-responder use from PREVA	£3,556	£3,899	-£343
25%	No response loss post month 2	gammaCore non-responder use from PREVA	£3,077	£3,899	-£821
25%	Constant rate of response loss	SoC non-responder use from PREVA	£3,643	£3,899	-£256
25%	Constant rate of response loss	gammaCore non-responder use from PREVA	£2,883	£3,899	-£1,016
25%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	£3,642	£3,899	-£256
25%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	£2,893	£3,899	-£1,006
40%	No response loss post month 2	SoC non-responder use from PREVA	£3,505	£3,899	-£394
40%	No response loss post month 2	gammaCore non-responder use from PREVA	£2,643	£3,899	-£1,256
40%	Constant rate of response loss	SoC non-responder use from PREVA	£3,509	£3,899	-£390
40%	Constant rate of response loss	gammaCore non-responder use from PREVA	£2,305	£3,899	-£1,594
40%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	£3,512	£3,899	-£387
40%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	£2,321	£3,899	-£1,578
50% using means	No response loss post month 2	SoC non-responder use from PREVA	£3,795	£3,899	-£104
50% using means	No response loss post month 2	gammaCore non-responder use from PREVA	£3,795	£3,899	-£104
50% using means	Constant rate of response loss	SoC non-responder use from PREVA	£3,797	£3,899	-£101
50% using means	Constant rate of response loss	gammaCore non-responder use from PREVA	£3,797	£3,899	-£101

Responder definition	Response loss assumption	Non-responder use assumption	gammaCore plus SoC	SoC	Difference
50% using means	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	£3,799	£3,899	-£100
50% using means	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	£3,799	£3,899	-£100
50%	No response loss post month 2	SoC non-responder use from PREVA	£3,448	£3,899	-£450
50%	No response loss post month 2	gammaCore non-responder use from PREVA	£2,972	£3,899	-£926
50%	Constant rate of response loss	SoC non-responder use from PREVA	£3,509	£3,899	-£390
50%	Constant rate of response loss	gammaCore non-responder use from PREVA	£2,881	£3,899	-£1,018
50%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	£3,509	£3,899	-£390
50%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	£2,887	£3,899	-£1,012
65%	No response loss post month 2	SoC non-responder use from PREVA	£3,387	£3,899	-£512
65%	No response loss post month 2	gammaCore non-responder use from PREVA	£3,123	£3,899	-£776
65%	Constant rate of response loss	SoC non-responder use from PREVA	£3,462	£3,899	-£437
65%	Constant rate of response loss	gammaCore non-responder use from PREVA	£3,153	£3,899	-£746
65%	Reduce probability of response loss by fixed percentage	SoC non-responder use from PREVA	£3,461	£3,899	-£438
65%	Reduce probability of response loss by fixed percentage	gammaCore non-responder use from PREVA	£3,153	£3,899	-£746
25%	No response loss post month 2	SoC non-responder use from PREVA	£3,556	£3,899	-£343
40%	No response loss post month 2	SoC non-responder use from PREVA	£3,505	£3,899	-£394
50%	No response loss post month 2	SoC non-responder use from PREVA	£3,448	£3,899	-£450
65%	No response loss post month 2	SoC non-responder use from PREVA	£3,387	£3,899	-£512

9.5.8 Results of the probabilistic sensitivity analysis described in Table C15

Calculated using the base case assumptions (≥50% response definition, no response loss after 2 months, abortive medication use from PREVA SoC arm for non-responders).

Table C21: Results of probabilistic sensitivity analysis

	Total per patient cost (£)
gammaCore plus SoC	£3,427.43
SoC	£3,864.13
Difference	-£436.70

9.5.9 Main findings of each of the sensitivity analyses

In general, sensitivity analyses supported the overall conclusion that using gammaCore in patients with cCH refractory to SoC medication can lead to substantial costs savings, primarily due to reduction in the use of sumatriptan and inhaled oxygen. The only scenario in which gammaCore was no longer cost saving was when the abortive medication use in the SoC arm of the model was set to its lower 5% estimate, leading to incremental costs in the gammaCore arm of £103. Assuming the upper 95% estimate of abortive medication use for gammaCore responders (any model cycle) and non-responders using gammaCore (relevant to evaluation period only) significantly reduced cost differences between the two arms, but still lead to cost savings for gammaCore overall.

Multi-way scenario analyses also lead to cost savings under all assumptions. As one would anticipate, more stringent response definitions lead to greater cost savings. Under the 50% definition, using alternative sources of resource as assumed by Morris et al., 2016 (mean use from gammaCore arm for responders; mean use from the SoC arm for non-responders), resulted in lower cost savings. This can be expected, as the medication use data was not stratified according to whether patients achieved a 50% reduction in attack frequency, as was done for this analysis.

Assuming no loss of response over the longer term also resulted in greater cost savings when gammaCore non-responders were assumed to revert to medication use observed in the SoC arm, highlighting that sustained response to gammaCore results in sustained cost savings.

Assuming that gammaCore non-responders off treatment revert back to their baseline resource use is more complex to interpret, as this relates to potential differences between responders and non-responders at baseline. In general, cost savings were greater when gammaCore non-responders were assumed to revert back to their observed baseline resource use, suggesting that non-responders may have used less abortive medication at baseline than patients on average in the SoC arm. This was also reflected in the greater cost savings observed when assuming loss of response over the longer term in this scenario, as non-responders were reverting back to lower use than the SoC arm without the incurring the costs of gammaCore. In general it would suggest that gammaCore is particularly beneficial in patients who are heavier users of abortive medicine, though further statistical analysis on patient-level data would be required.

Assuming that responders in the SoC arm during the first cycle consumed the same quantity of abortive medication as those in the gammaCore arm had no material impact on results.

The probabilistic results were closely aligned with the deterministic ones, with probabilistic cost savings of £436.70 vs. £450.42 in the deterministic base case. gammaCore plus SoC had an 88.5% probability of being cost-saving vs. SoC alone.

9.5.10 Key drivers of the cost results

The most influential parameter in the cost analysis was the frequency of sumatriptan doses in non-responders of the SoC arm of the model. This value informs the SoC arm in its entirety apart from during the first cycle, when a small proportion of patients are responders. It also informs the resource use of non-responders in the gammaCore arm who have discontinued gammaCore.

This was the only parameter which resulted in increased costs in the gammaCore arm vs. SoC, when set to its lower bound value, by £103. However, cost differences when varying this parameter were heavily skewed towards cost savings, with up to £1,223 in savings possible when varying to the upper bound value.

Other parameters underpinning sumatriptan use in the model were also influential, with cost differences between the lower and upper value of up to £668, but no lower or upper bound values resulted in any other outcome other than cost savings. These parameters predictably pertained to sumatriptan use in gammaCore responders, and in gammaCore non-responders during the first 3 months of treatment (who are still responding to gammaCore, but not at the threshold that defines a responder).

As one would anticipate, raising the threshold for continued treatment with gammaCore (responder definition) resulted in greater cost savings, as patients who continue treatment have greater reduction in abortive medication use to offset gammaCore costs. Cost savings were achieved however, at a response definition of ≥25%, a level considered clinically meaningful in the Marin study.

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Any analysis of subgroups and how these subgroups were identified

No subgroup analyses were conducted, for reasons explained in section 9.1.2.

9.6.2 Characteristics of patients in the subgroup(s)

Not applicable.

9.6.3 How the subgroups were included in the cost analysis

Not applicable.

9.6.4 Results of the subgroup analysis/analyses, if conducted

Not applicable.

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The model structure used for the cost analysis was adapted from that reported in a peer reviewed publication by Morris et al. Adaptations were quality checked by a second health economist. The model assumptions and results were validated with clinical experts.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

One published study by (Morris et al. 2016) that compared use of gammaCore plus SoC vs. SoC reported cost savings after one year of 414 euros. This analysis differed from the current one in that:

- The first 3 months of gammaCore treatment were not free and the German list price was used
- Patients could discontinue gammaCore on a monthly basis (as opposed to 3-monthly)

- Abortive medication use in the Morris analysis was obtained from data summarised per trial arm as opposed to summarised by responder vs. non-responder: Abortive medication use of responders in the gammaCore arm of Morris et al. was the mean of all patients in the gammaCore arm as opposed to only those patients defined as responders and thus would be expected to under predict potential cost savings. This is reflected in the results of section 9.5.7.

- Abortive medication use of non-responders in the gammaCore arm of Morris et al. was the mean of all patients in the SoC arm as opposed to those patients defined as non-responders in the gammaCore arm

- 4 'late responders' who responded during the extension phase of PREVA were included in the base analysis of Morris et al. We were unable to identify these patients in the present analysis.

In summary, Morris et al. modelled costs that were less generalisable to clinical practice and abortive medication use conditional on responder status was less robust.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The cost analysis is relevant to cCH patients who are using gammaCore preventatively with possible on top acute use. While the company acknowledges that episodic use has not been addressed in the cost analysis, the Marin study would suggest that either the number of patients who would be offered gammaCore in practice would be very low, and/or the majority would not continue using gammaCore past the free 3-month evaluation period and would therefore not incur treatment costs.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The clinical data used by the model were sourced from a robust and clinically relevant RCT in cCH, from which data on abortive medication use were available directly. However, because the PREVA study lacked a sham treatment group, the degree to which the placebo effect might have contributed to the cost savings of gammaCore is unclear.

The PREVA study provided data from an 8-week period, which were extrapolated to assess cost-effectiveness over 1 year. Although there have been few cost-effectiveness evaluations of neuromodulation techniques for the treatment of primary headache disorders, some studies have included time horizons of up to 5 years (see section 8.2.1). Considering the time frame of PREVA, a 1-year time horizon was chosen for this analysis to preserve robustness and to avoid introducing unnecessary uncertainty.

Robustness of the results was explored using extensive sensitivity analyses, including exploration of different definitions of a response determining ongoing gammaCore treatment. The least conservative response definition that was still cost saving was a 25% reduction in attack frequency, which is much lower than the 64% reduction observed in the Marin UK observational study.

A limitation of the analysis was that patients were randomised on the basis of CH attacks but not by resource use. There is therefore the risk of potential imbalance affecting the results, particularly for sumatriptan which is particularly expensive. This was addressed to some extent by using data from the SoC arm to inform the resource use of gammaCore non-responders who had discontinued treatment. Matched abortive medication use was not available for all patients reporting attack frequency and the results may be subject to bias from incomplete outcome data.

In the UK Marin study, patients were experiencing 26.6 attacks/week at baseline. Patients in the PREVA trial experienced 67.3 (nVNS plus SoC) to 73.9 attacks (SoC only) at baseline over a 4-week period. This would suggest that patients who are offered gammaCore in the UK may be more severe than

those recruited in PREVA. Furthermore, all patients in the Marin study were using abortive medication vs. 90% of patients in PREVA. While the number of patients using different types of abortive medication was captured in the Marin study, the quantity of units consumed were not captured consistently enough to permit calculation of cost savings. Thus, the abortive medication use at baseline, and the absolute reduction in use and resultant cost savings may be underestimated in this cost analysis.

The decreased use of oxygen was captured as reduced refill charges only. However, 9 patients (33%) in the Marin study discontinued oxygen use altogether. There could therefore be additional rental cost savings of approximately £200 per year (East of England priorities advisory committee. 2017) that were not captured in the cost analysis.

The current cost projections included only the costs associated with the use of abortive treatments. This suggests that the analysis is conservative, as data on additional health care resource use (e.g. clinic visits, hospitalisations) as well as ongoing use of preventative medication such as verapamil would likely lead to a disproportionate cost increase for the SoC-alone group.

As with patients with epilepsy (Elliott et al. 2011) evidence suggests that patients with headache may have improved response to VNS with longer-term treatment (Silberstein. 2014), (Yuan and Silberstein. 2017). Although increases in response rate with long-term VNS have yet to be explored in CH, the current analysis could be viewed as conservative because the duration of PREVA may not have allowed demonstration of the full benefit of gammaCore at the 3-month evaluation time point.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The model included only the costs associated with the use of abortive treatments, which was not available from a number of patients who provided matched attack data. A patient-level regression analysis to estimate the

relationship between abortive medication use, attack frequency and baseline characteristics may be warranted.

A real-world study collecting healthcare resource use, as well as preventative medication use would capture further potential costs savings outside of abortive medication. A real-world study would also permit more robust evaluation of response rate and medication use at the 3-month evaluation period (in the Marin study the mean duration of the evaluation period was 7.6 (0.9–27.5) months). Analysis of abortive medication use in the Marin study in patients with complete consumption data would provide estimates of cost savings in a population that is more generalisable in terms of severity.

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10 Appendices

10.1 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

10.1.1 Databases searched and the service provider used (including at least Medline, Embase, Medline (R) In-Process, and The Cochrane Library)

The Medline and Medline (R) In-Process databases were searched through PubMed.gov using the Entrez service provider. The Embase and Cochrane Library databases were searched using the OVID and Wiley service providers, respectively.

10.1.2 Date on which the search was conducted

The search was conducted on 21 February 2019.

10.1.3 Date span of the search

Articles published between 1 January 2005 and 21 February 2019 were included in the search results because 2005 was the year the sponsor of non-invasive vagus nerve stimulation (nVNS) was founded.

10.1.4 Complete search strategies used (including all search terms and relationship between the search terms)

Search terms were “cluster headache” AND (“non-invasive vagus nerve stimulation” OR “noninvasive vagus nerve stimulation” OR “gammaCore” OR “transcutaneous vagus nerve stimulation”). In the PubMed search, “humans” was used as a MeSH term, language was specified as English, and no search limits on article type were defined to ensure the identification of all relevant studies, including clinical trials and real-world and observational studies. In Embase, the Title or Abstract field was used to search for the terms, and results filters were applied for diseases (chronic cluster headache, cluster headache, and episodic cluster headache), study types (humans), and

publication types (article). In the Cochrane Library, the All Text field was used to search for the terms, and a search limit was defined to identify trials only.

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases

The search for published studies was conducted in public databases only.

10.1.6 Inclusion and exclusion criteria

Search results from each database were cross-referenced, and duplicates were removed to create a master list of unique records for screening. Published conference abstracts and any ClinicalTrials.gov records were excluded to avoid duplication in the corresponding published article; those without a corresponding published article were reserved for the unpublished data sections. Records for Epubs were excluded if search results also contained a corresponding print publication, also to avoid duplication. Search results that clearly did not represent studies of nVNS use in cluster headache on the basis of the article title and abstract (e.g. healthy subjects) were also excluded at this stage.

The eligibility of full-text articles was then assessed for the remaining records. Studies included were required to be clinical trials evaluating nVNS for the treatment or prevention of cluster headache. Review articles were excluded. Articles reporting only post hoc analyses or those not reporting primary prespecified data of a study were excluded and discussed only in section 7.4.2 (i.e. data from a single study drawn from more than one source).

10.1.7 Data abstraction strategy

Articles determined to be eligible for qualitative synthesis were reviewed, and each item detailed in this template was extracted and entered directly into the document. Data abstraction was verified by a second reviewer for accuracy and completeness.

10.2 Appendix 2: Search strategy for adverse events (section 7.7.1)

10.2.1 Databases searched and the service provider used (including at least Medline, Embase, Medline (R) In-Process, and The Cochrane Library)

The Medline and Medline In-Process databases were searched through PubMed.gov using the Entrez service provider. The Embase and Cochrane Library databases were searched using the OVID and Wiley service providers, respectively.

10.2.2 Date on which the search was conducted

The search was conducted on 6 March 2019.

10.2.3 Date span of the search

Articles published between 1 January 2005 and 6 March 2019 were included in the search results because 2005 was the year the sponsor of nVNS was founded.

10.2.4 Complete search strategies used (including all search terms and relationship between the search terms)

Search terms were (“headache” OR “migraine” OR “cardiovascular”) AND (“non-invasive vagus nerve stimulation” OR “noninvasive vagus nerve stimulation” OR “gammaCore” OR “transcutaneous vagus nerve stimulation”) AND ("safety" OR "safe" OR "tolerability" OR "side effect" OR "adverse event"). In the PubMed search, “humans” was used as a MeSH term, language was specified as English, and no search limits on article type were defined to ensure the identification of all relevant studies, including clinical trials and real-world and observational studies. In Embase, the Title or Abstract field was used to search for the terms, and results filters were applied for diseases (migraine, headache, chronic cluster headache, episodic migraine, cluster headache, transformed migraine, migraine without aura, primary headache, episodic cluster headache, menstrual migraine, migraine

with aura, and drug induced headache), study types (humans), and publication types (article). In the Cochrane Library, the All Text field was used to search for the terms, and a search limit was defined to identify trials only.

10.2.5 Details of any additional searches, such as searches of company or professional organisation databases

The electroCore Clinical Library (available at ecorelibrary.com) is an online company database containing a selection of posters presented at various conferences from 2014 through 2017. This library was manually scanned for safety studies of nVNS focused on cardiovascular effects because no such studies were identified during the published or unpublished study searches. The applicable study identified was reserved for the unpublished data sections.

10.2.6 Inclusion and exclusion criteria

Search results from each database were cross-referenced, and duplicates were removed to create a master list of unique records for screening. Published conference abstracts were excluded to avoid duplication of the corresponding published article; those without a corresponding published article were reserved for the unpublished data sections. Records for Epubs were excluded if search results also contained a corresponding print publication, also to avoid duplication. Based on the article title and abstract, search results that clearly did not represent safety studies of nVNS use in headache conditions or safety studies of nVNS that focused on cardiovascular effects were also excluded at this stage, as were the 3 published studies of nVNS for cluster headache identified and appraised in sections 7.1 to 7.6 that were also designed to evaluate safety (to avoid duplication).

The eligibility of full-text articles was then assessed for the remaining records. Studies selected were required to be clinical studies that included quantitative primary safety evaluations of nVNS in patients with headache conditions or safety studies of nVNS focused on cardiovascular effects. Review articles were excluded. Articles reporting only post hoc analyses of a study were

excluded, as were studies that did not comprehensively report adverse events.

10.2.7 Data abstraction strategy

Articles determined to be eligible for qualitative synthesis were reviewed, and each item detailed in this template was extracted and entered directly into the document. Data abstraction was verified by a second reviewer for accuracy and completeness.

10.3 Appendix 3: Search strategy for economic evidence (section 8.1.1)

10.3.1 Specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter)

A systematic literature review was conducted from the following sources to identify studies reporting economic models and cost analyses in cluster headache.

- MEDLINE and Medline in process via PubMed;
- EMBASE and EMBASE Alert via ProQuest;
- CRD (DARE, NHS EED, HTA)
- www.heoro.com

10.3.2 Date on which the search was conducted

The database searches were run on 20 March 2019.

10.3.3 Date span of the search

No date limit was set for the searches.

10.3.4 Complete search strategies used (including all search terms and relationship between the search terms)

Appendix Table 1: MEDLINE, MEDLINE in process via PubMed

Search	Search string	Number of hits
Limits	Publications with abstracts in humans	
1	Cluster Headache[Mesh] OR "cluster headache"[tiab]	2235
2	"Cost-Benefit Analysis"[Mesh] OR "economics" [Subheading] OR economic*[tiab] OR (cost*[tiab] AND (efficacy[tiab] OR effectiveness[tiab] OR benefit[tiab] OR utilit*[tiab] OR minimi*[tiab] OR analys*[tiab]) OR "monte carlo"[tiab] OR markov[tiab] OR ((cost*[tiab] OR economic*[tiab] OR budget*[tiab]) AND model*[tiab]) OR "discrete event simulation"[tiab] OR "technology assessment"[tiab]	410309

Search	Search string	Number of hits
3	1 AND 2	60

Appendix Table 2: EMBASE, EMBASE alert (via ProQuest)

Search	Search string	Number of hits
Limits	Publications with abstracts in humans	
1	EMB.EXACT.EXPLODE("cluster headache") OR AB,TI("cluster headache")	4227
2	MJEMB.EXACT("pharmacoeconomics") OR (AB,TI((economic* OR cost* OR budget*) AND (model)) OR (AB,TI(cost AND (efficacy OR effective* OR benefit OR utilit*)) OR "monte carlo" OR markov OR "discrete event simulation" OR "technology assessment"))	312222
3	1 AND 2	80

Appendix Table 3: CRD database

Search	Search string	Number of hits
Limits	None	
1	"cluster headache"	19

Appendix Table 4: Heoro.com database

Search	Search string	Number of hits
Limits	None	
1	Disease: Cluster headache Study type: Economic model studies	5

10.3.5 Details of any additional searches, such as searches of company or professional organisation databases

None.

10.4 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The resource use included in the cost analysis related only to use of abortive medication, which was sourced directly from the PREVA study. No searches were therefore carried out.

10.4.1 Specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter)

Not applicable.

10.4.2 Date on which the search was conducted

Not applicable.

10.4.3 Date span of the search

Not applicable.

10.4.4 Complete search strategies used (including all search terms and relationship between the search terms)

Not applicable.

10.4.5 Details of any additional searches, such as searches of company or professional organisation databases

Not applicable.

10.4.6 Inclusion and exclusion criteria

Not applicable.

10.4.7 Data abstraction strategy

Not applicable.

11 Related procedures for evidence submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- An electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- A copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- An executable electronic copy of the cost model has been submitted
- The checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

MT323 GammaCore for Cluster Headaches

1st draft comments added:

Pre-publication fact check comments added:

Expert contact details

Expert #1	Fayyaz Ahmed (Consultant Neurologist): British Association for the Study of Headache
Expert #2	Dr Mark Weatherall (Consultant Neurologist): Buckingham Healthcare NHS Trust
Expert #3	Alok Tyagi (Consultant Neurologist) Association of British Neurologists; British Association for the Study of Headaches
Expert #4	Dr Brendan Davies (Consultant Neurologist and Clinical Lead) Midlands regional Headache Clinic
Expert #5	Dr Jane Anderson (Consultant Neurologist) Cambridge University Health Foundation Trust

Please answer the following questions as fully as possible to provide further information about the technology and/or your experience

1	Please describe your level of experience with the technology, for example: − Are you familiar with the technology? − Have you used it? − Are you currently using it?	**Expert #1** I have been using Gammacore for at least 7 years since it was CE Marked and the company started to provide free treatments for trial. I was also involved in the clinical trials on patients with cluster headache and migraine – some of which have already been published. Since then I have used the technology in around 50 patients mainly sponsored for a three month free trial by the company of which at least 30% showed some improvement. For such patients I had applied for NHS funding through Individual Funding Request (IFR). Around 20% of IFR were given approval and the remainder 80% were turned down.

	− Have you been involved in any research or development on this technology? − Do you know how widely used this technology is in the NHS?	**Expert #2** I was first introduced to the GammaCore VNS device in 2013. We started to use it at Charing Cross Hospital in selected patients at around that time. Early experience was mixed (probably because we initially tried it in predominantly in patients with refractory migraine) and we stopped using it for a couple of years. Following the publication of a number of papers indicating the potential utility of the device in cluster headache, we started to use it again more regularly from 2016 onwards. Since my move in early 2018 to Buckinghamshire Healthcare NHS Trust, I have been looking after a much smaller number of cluster headache patients, and so I have been using it less frequently recently. This change is not due to any disenchantment with the efficacy of the device or any problems with the literature. I have had frequent conversations with GammaCore personnel about the development of the device, but have not been formally involved in research. The technology is I believe used in a number of specialist headache clinics across the UK. **Expert #3** Yes I am very familiar with the gammacore device and have used it on a regular basis for a number of years. I was PI for the clinical trials of gammacore in episodic and chronic cluster headaches as well as chronic migraine. I currently use it as an adjunctive treatment for acute and preventive treatment for cluster headaches. This technology is not very widely used in NHS Scotland but is used elsewhere in the UK. **Expert #4** I am familiar with the technology i.e. the Gammacore device and have used it and continue to use it for the treatment of several primary headache disorders. I am constrained from starting it for new patients by the fact that it now has to be self-funded by patients as it is not currently comissioned as a therapy by the NHS.

		I use this device mainly for the treatment of Cluster headache but I have experience of using the technology in other Trigeminal autonomic cephalalgias (TACs) similar to cluster headache such as Hemicrania Continua and Paroxysmal hemicrania (where Indometacin can no longer be used due to side effects, contraindications or bleeding problems).I have found it very useful for the treatment of cluster headache as both a preventive therapy and an acute abortive therapy with good tolerability compared to existing therapies and in patients where these therapies either have not worked or not been tolerated. We have usedthis technology in several patients with medically refractory chronic migraine with little if any benefit in contrast to using it in Cluster headache & other TACs I have not been involved in research trials of this device but have had initially free access to the device for several patient's refractory to other treatments for their cluster headache who have subsequently gone on to have CCG funded devices when the cost saving on acute treatments were seen as part of the device preventative efficacy. These patients have been written up a case series/ The technology is largely used by Neurologists with a specialist interest in Headache disorders in secondary care specialist headache clinics in the UK. It is not widely used by general neurologists due to both lack of awareness and the logistics of getting it funded. I have used this device at our centre in over 50-80 patients over the last 4 years with only about 20 patients continuing on therapy due to efficacy. **Expert #5** Yes I am familiar and have used this technology on a small cohort of patients and continue to do so. This technology due to cost limitations and experience base is typically restricted to tertiary headache centres and private practise.
2	Has the technology been superseded or replaced?	**Expert #1** Non-invasive neuromodulation has been proposed as an alternative treatment to pharmaceutical agent in the last decade. Some of the earlier treatments involved equipment that were big and difficult to carry around. Arrival of Gammacore provided an option of portable equipment that one could carry so they could be used as and when needed wherever you are. **Expert #2**

		No **Expert #3** No **Expert #4** There is a new model of the device with a rechargeable battery and a “sim” like card that is time or number of treatments limited as part of the companies contracting scheme for patients who self-fund the device. The main features of the device have not changed to my knowledge. **Expert #5** No

Current management

3	How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?	**Expert #1** I had always thought that if non-invasive neuromodulation was successful they would gradually replace the traditional pharmaceutical treatments. So far the treatment seems to be effective in few patients although a large number of prospectively suitable patients were denied treatment as the treatment is not funded on the NHS **Expert #2** Non-invasive VNS stimulation is a completely novel approach to the management of primary headache disorders. **Expert #3** This is a novel concept and is very patient and user friendly in terms of almost a complete absence of side effects. **Expert #4** I was initially very sceptical abut this technology and with usage and subsequent basic science research on its possible mechanism of action have slowly been convinced it has a place in the current standard of care/ The device is extremely innovative. It is a non-drug therapy, is easy to use and very patient friendly with no need for safety monitoring It is patient administered. Most of the current standard of care drug preventive therapies have little scientific rationale for their

		use, are challenging to monitor due to safety reasons e.g. Verapamil and ECG monitoring, Lithium & toxicity & drug level monitoring. It has introduced the first evidenced based therapy for the treatment of cluster headache with RCT evidence for more than 20 years **Expert #5** This is a novel approach with current standard of care being restricted to oral/injectable drugs with often limiting systemic side effects. For those with high frequency attacks standard of care for acute management involves use of oxygen and this is limiting both in cost and portability. External transcutaneous vagal nerve stimulation is a novel approach with little significant side effects and is an extremely portable technology and for both of these reasons is attractive to patients
4	Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?	**Expert #1** There are two other competing non-invasive neuromodulation treatments available although none of those are funded on the NHS either. One is transcranial magnetic stimulation (TMS) that involves a fairly large device that is often difficult to carry. It is equally effective but the mode of action is different. TMS generates magnetic waves that disturb the brain in a nicer way to terminate or reduce the severity of migraine attacks. The other is cephaly that is available to buy through the internet. That involves stimulation of the supratrochlear and supraorbital nerves through skin application over the forehead. **Expert #2** No **Expert #3** An external trigeminal nerve stimulator is available but in my experience is not a very effective treatment for migraine. Gammacore is the only device available for cluster headache patients. This group is severely disabled by their condition and this is a valuable addition to the treatment options. **Expert #4** No – I am unaware of any other external vagal nerve stimulator devices like this for Cluster headache **Expert #5**

		No

Potential patient benefits

5	What do you consider to be the potential benefits to patients from using this technology?	**Expert #1** Lack of side effects, better tolerance **Expert #2** The GammaCore VNS device has proven efficacy in an invariably severe and often refractory headache disorder – cluster headache. It is safe and straightforward to use. It can be used alongside current acute and preventive treatment options with no interactions. **Expert #3** Side effect free, more or less. Safe Effective **Expert #4** • Ease of use & portability for patients • Lack of adverse effects compared to other preventative therapies • Cost and ability to reduce acute treatment drug costs for injectable sumatriptan for device responders • Reduced impact of Cluster headache & TACs on patients quality of life • Lesser consultation rates as device can be charged remotely and controlled in terms of device stimulation (on/off) remotely via sim **Expert #5** Acute treatment of attacks (episodic cluster) Reducing frequency of attacks Reduced side effects of therapies

		Good tolerability and compliance
6	Are there any groups of people who would particularly benefit from this technology?	**Expert #1** Anyone could benefit but those with adverse events to pharmaceutical intervention or in whom many drugs have failed would benefit most. Also in those where acute or preventive treatments may be contraindicated such as patients with ischaemic heart disease or pregnant women may choose to try this. **Expert #2** The VNS device is believed to be safe to use in pregnancy and breastfeeding. It may also be particularly useful in people with known cardiovascular or cerebrovascular disease, or significant risk factors for these, in whom many of the existing options are contra-indicated. **Expert #3** Chronic Cluster headache sufferers **Expert #4** Patients with Cluster headache other TACs. Other patient groups need more research on effectiveness from proper blinded Randomised controlled trials before I wold advocate for this technology in other headache disorder groups. **Expert #5** Cluster headache patients (both episodic and chronic) and other patients with rarer trigeminal autonomic cephalalgias. Those where current standard of care is insufficient to effect optimal control or where standard lines of therapies are either contraindicated or not tolerated (eg. patient needle phobic or with intolerable side effects).
7	Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	**Expert #1** Not every patient will respond to this treatment although if this was to be made available on the NHS, one could try this treatment in those where first line treatments have failed. This is mainly because of the cost of technology. I would place this treatment very similar to Botox. Only those who have failed to three treatments are given this treatment in the secondary care. **Expert #2**

		There is good clinical evidence of efficacy in a disorder which very often leads to hospital admissions. There is a potential for it to reduce both emergency admissions and elective admissions for intravenous treatments such as IV dihydroergotamine. **Expert #3** Absolutely. I have had experience of several patients reverting to episodic cluster headaches by using this device. **Expert #4** Yes – It has the potential to be a second or 3rd treatment in the pathway for the prevenative treatment of Cluster Headache especially in advance of Lithium. This might not only improve Cluster headache treatment outcomes but reduce the need for long term repeated clinic follow-up for some, reduce exposure to other preventative drugs with more toxic sided effects, reduce the need for onward referral to invasive neurostimulation therapies which are much more expensive for Cluster headache such as Occipital nerve stimulation, Deep Brain stimulation & Sphenopalantine ganglion stimulation for refractory chronic Cluster headache **Expert #5** Yes. This is an extremely disabling condition where current treatment options are very limited. With efficacy in both aborting attacks and reducing attack frequency this will potentially result in fewer hospital and primary care visits as patients will be better able to manage their bouts with reduced demand for triptans, oxygen supply and transitional steroids or greater occipital nerve blocks. Patients who struggle to tolerate standard care medications and can be high users of the service will also have an alternative option to limit these contacts.

Potential system impact

8	What do you consider to be the potential benefits to the health or care system from using this technology?	**Expert #1** Availability of a non-invasive treatment option for those that appear to be refractory to first line agents where more invasive and costly treatments are being considered (such as deep brain stimulation, occipital nerve stimulator, sphenopalatine ganglion stimulation) **Expert #2** GammaCore VNS provides an additional validated option for the management of the most severe primary headache disorder known. Cluster headache is not as common as migraine, but it does cause significant levels of disability in an age group at their potential maximum utility to society as a whole. **Expert #3** This is a self administered treatment that, when successful, minimises admissions / visits to GPs or hospitals. It is cost effective as it reduces, significantly, the use of injectable sumatriptan which is an expensive treatment. **Expert #4** Better outcomes from prevention, reduced acute sumatriptan injection drug costs, possible reduced reattendance costs for secondary care specialist Outpatients, **Expert #5** Better control of this difficult condition leading to less crises non-elective hospital admissions and when effective reduced hospital and primary care contacts Improved management would have significant impact on non-direct healthcare indices and may have substantial benefit to the individual's quality of life.
9	Considering the care pathway as a whole, including initial capital and possible future	**Expert #1**

	costs avoided, is the technology likely to cost more or less than current standard care, or about the same?	The technology would cost more than standard of care but we are only recommending the treatment to those who are refractory to treatment and are being considered for more expensive and invasive treatment options. **Expert #2** I do not have data on this, but I see no reason to think that the use of this technology in patients who respond to it will lead to the use of additional resources, as it can be presumed that other ineffective treatments could be stopped. **Expert #3** Perhaps less **Expert #4** Likely to cost less if effective as it would reduce acute attack frequency and severity and reduce the need for expensive injectable acute therapy, oxygen prescriptions and deliveries. There may be a replacement cost of the intermittent review of responders to see if the device is still needed. This would likely occur with any therapy anyway/ **Expert #5** This is a costly treatment but in those where it is effective the saving from subcut sumatriptan/ oxygen consumption and reduced health contact costs can offset the cost such that it requires marginal extra investment –in some individual cases this will be cost neutral. The marginal investment that would be required would be considered a valuable investment for the impact on quality of life this may make.
10	What do you consider to be the resource impact from adopting this technology?	**Expert #1**

	Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?	The technology is extremely easy to use and could be taught through a video. No additional appointment time required than a normal consultation and further follow ups could be done by the nurses. **Expert #2** I do not have data on this, but I see no reason to think that the use of this technology in patients who respond to it will lead to the use of additional resources, as it can be presumed that other ineffective treatments could be stopped. **Expert #3** Don't think it shifts the care but certainy improves patient's lives **Expert #4** There would be aneed for more Headache nurse specialist staff to be involved in the initiation, assessment of treatment response and periodic review to determine ongoing need or cessation for the device technology. It is conceivable that some monitoring could be remotely via telephone or using digital technology in the future as part of the device usage and treatment response monitoring process **Expert #5** Likely avoid inpatient contacts and anticipate reduction in health care contacts
11	Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?	**Expert #1** The treatment is suited for secondary / tertiary care headache clinics for initiation but could be monitored in primary care. **Expert #2**

		Expert #3 No **Expert #4** Very little **Expert #5** It does require education of the clinician/ nurse as to how to use the device so that they can subsequently provide patient education to enable use of the device appropriately –this has been provided by electrocore and additional support given to patients when they are learning self-treatment as needed
12	Are you aware of any safety concerns or regulatory issues surrounding this technology?	**Expert #1** None **Expert #2** Nothing significant. **Expert #3** No **Expert #4** No

		Expert #5 None

General advice

13	Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.	**Expert #1** None **Expert #2** This is covered in Question 1. **Expert #3** This is an invaluable addition to the treatment options for cluster headache sufferers and is offered routinely to patients who do not respond to standard treatments **Expert #4** I would be keen to see this device adopted as a commissioned device technology for the treatment of cluster headache based on my experience of its usage for Cluster headache and TACs. I would not advocate its usage in Migraine from an NHS commissioned basis unless better more robust trials to show both efficacy and cost effectiveness have been performed. **Expert #5**

Other considerations

14	Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population ?	**Expert #1** Difficult to estimate In my tertiary headache clinic set up where I see nearly 2000 patients per year referred from all over England, I will have around 200 patients eligible for treatment of which 30% would respond so wouldn't expect more than 60 people per year would be consuming NHS resources for this. **Expert #2** Cluster headache is said to affect about 1/200 people in the UK. This equates to 30,000 people. Many of these patients are undiagnosed. Many patients with a diagnosis will respond to existing treatments, but it would be reasonable to assume that at least 20-30% of patients have unmet clinical needs. **Expert #3** As an estimate this treatment would be trialed in 25-30 cluater headache sufferers each year. **Expert #4** In Our area with a population catchment area of approximately 1.5 million I would expect no more than 20-30 persons with Cluster headache might be considered for this deviceper year based on recent years' experience with managing cluster headache and our local referral population. **Expert #5** 20-40% of a small cohort (given that this is a relatively rare condition). Note many episodic cluster headache patients remain out-with secondary/tertiary care and the appeal of this device may result in further increase in those seeking assessment.

15	Would this technology replace or be an addition to the current standard of care?	**Expert #1** It has to be additional as it is reserved for refractory patient population rather than first line treatment strategy. **Expert #2** It is an addition to the current standard of care. **Expert #3** Addition **Expert #4** It would certainly add to standard of care as I would plan to consider using it as 2nd or 3rd line therapy in chronic Cluster headache. It wold likely therefore displace and possibly potentially replace some later therapies in the longer term. **Expert #5** Addition to current standard of care but its use may substantially reduce some aspects of standard care e.g. sumatriptan/oxygen use
16	Are there any issues with the usability or practical aspects of the technology?	**Expert #1** None **Expert #2** Not really. Most patients find it straightforward once shown how to hold it in the correct place.

		Expert #3 No **Expert #4** NO – not that I am aware of. Our patients have found it easy to use, they learnt how to sue it easily when educated about its usage by our headache Nurse Specialist **Expert #5** No- technology is easy to use and patient report is very positive (being in many preferred to injectable triptans, the equipment required for oxygen use etc.)
17	Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?	**Expert #1** No as far as this comes with mandatory funding following NICE recommendation. IPG has recommended this treatment but does not come with funding. **Expert #2** The main issue at present is funding, as there is no onus on funders to cover the costs of this treatment. **Expert #3** No **Expert #4** Funding availability from CCGs even after IPG approval from NICE. CCG argue this is not commissioned and only have agreed to time limited funding after submitted IFRs for device response cluster headache patients who have successfully responded to the device with

		concomitant reduction in acute drug costs and hospital visits. However repeated IFRs have not led to any policy of commissioned services even though the numbers are small. **Expert #5** At present the cost as this is not routinely covered by the NHS and for long term use mandates an IFR application which is both clinician time intensive and frequently rejected on the basis of lack of exceptionality.

Expert #2

18	Are you aware of any further evidence for the technology that is not included in this briefing?	**Expert #1** Not that I am aware of. **Expert #2** Unknown **Expert #3** No **Expert #4** No **Expert #5** ? Have ACT1 and ACT2 study been included which show its additional benefits in episodic cluster headaches (ACT 1 by Silberstein et al 2016 (8) 1317-32, ACT2 by Goadsby et al Cephalalgia 2017).
19	Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence	**Expert #1** We are about to start a trial in patients with chronic migraine. We were involved in the cluster headache study (ACT 1 and 2) which has been published as well as GM11 in episodic migraine which is not published yet. Yes **Expert #2**

	within the NICE process and will not be shared or published.	I have no data on this **Expert #3** We have local data that includes number of patients trialled and numbers who currently use the device. This can be provided if requested. **Expert #4** I have been a co-author on a small series of UK patients recently published with colleagues describing our outcomes and our experience of the device response in the UK in the Journal of Headache & Pain in Dec 2018 **Expert #5** No
20	Is there any research that you feel would be needed to address uncertainties in the evidence base?	**Expert #1** Looking at a real world data from prospective patients being treated and compared with the RCT data. **Expert #2** The evidence base for cluster headache is fairly clear. **Expert #3** No **Expert #4** Usage in Migraine, Post Traumatic Headache.

		Expert #5 I think current evidence base would support use. It would be useful to also have an evidence base and cost assessment analysis of those where this has not been added to standard care but used as a stand-alone therapy as this is extremely well tolerated as a treatment and currently our use is focused largely only in those where standard care alone is failing.

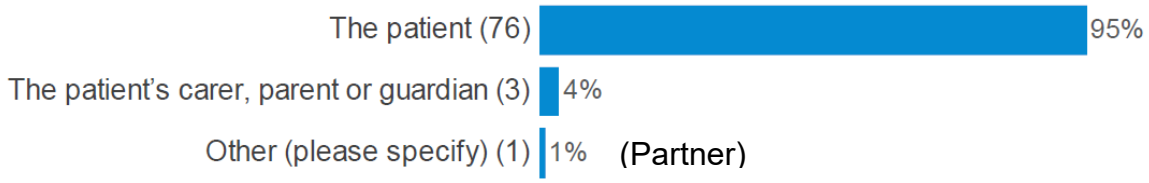
Results of NICE PIP patient survey – MT323 gammaCore for cluster headache

During April–May 2019, NICE's public involvement programme posted an online survey, 80 responses were received.

All responders confirmed that they read the information sheet provided which explains the purpose of the survey and how the information will be used. All responders consented to NICE using the information as described.

1. Responder demographics

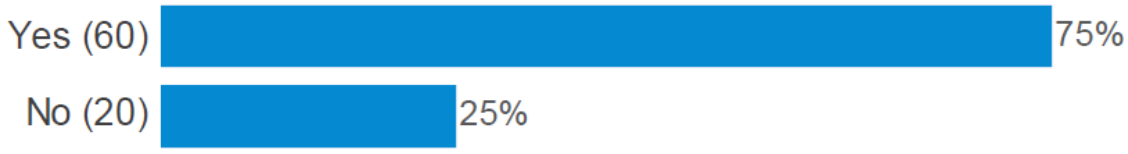
Are you (the person completing the questionnaire):



Mean age of responders was 48.5 years, range 20–80 years. 54% of responders were female and 46% were male.

2. Diagnosis

Have you been diagnosed with cluster headache?

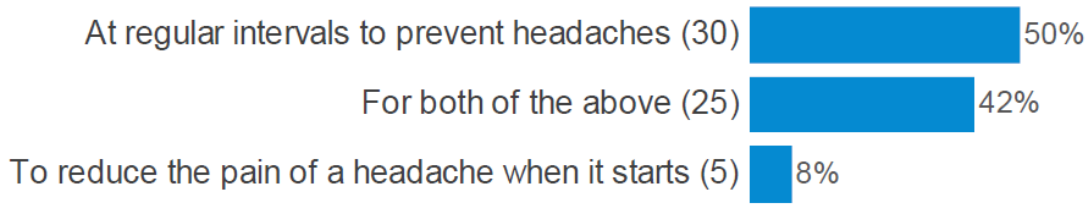


Responders that have not been diagnosed with cluster headache did not answer any further questions. Of the 60 responders diagnosed with cluster headache, 46 chronic cluster headaches and 12 had episodic cluster headaches.

3. Device usage

Responders had been using gammaCore for a mean of 411 days, range 1 week–5 years.

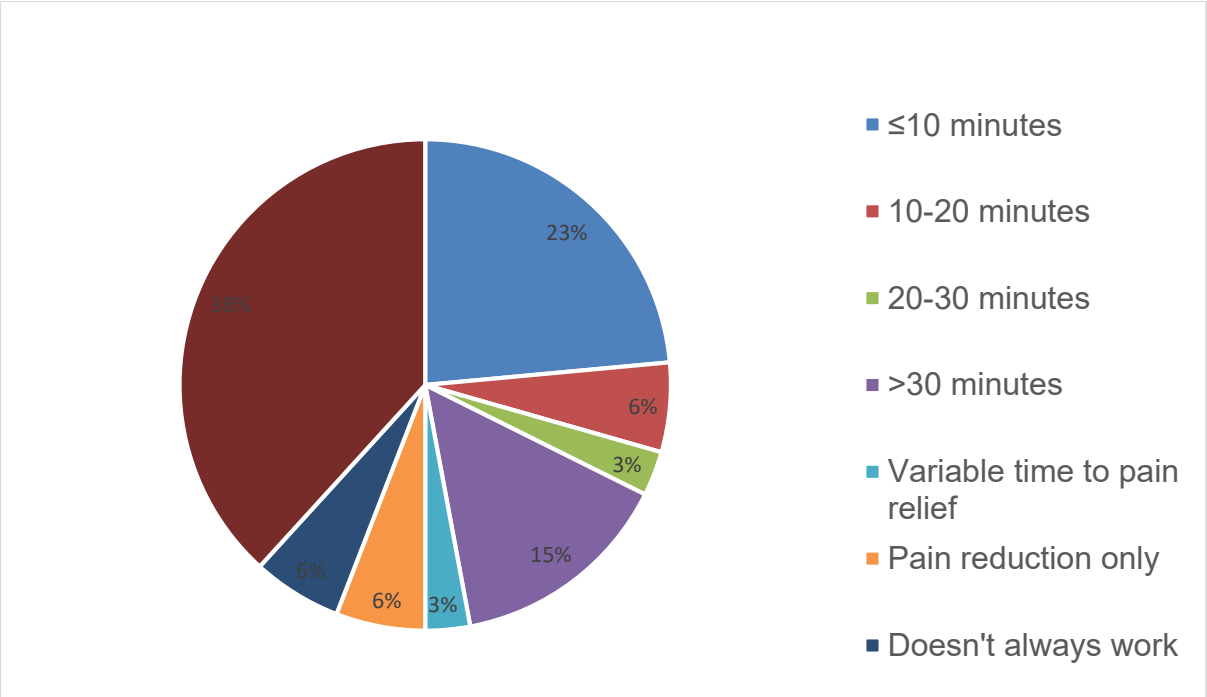
Do you use gammaCore to:



Responders stated that they used gammaCore every day, most responders used the device 2–4 times a day with some stating that they use it more frequently, one responder stated they use gammaCore up to 21 times a day.

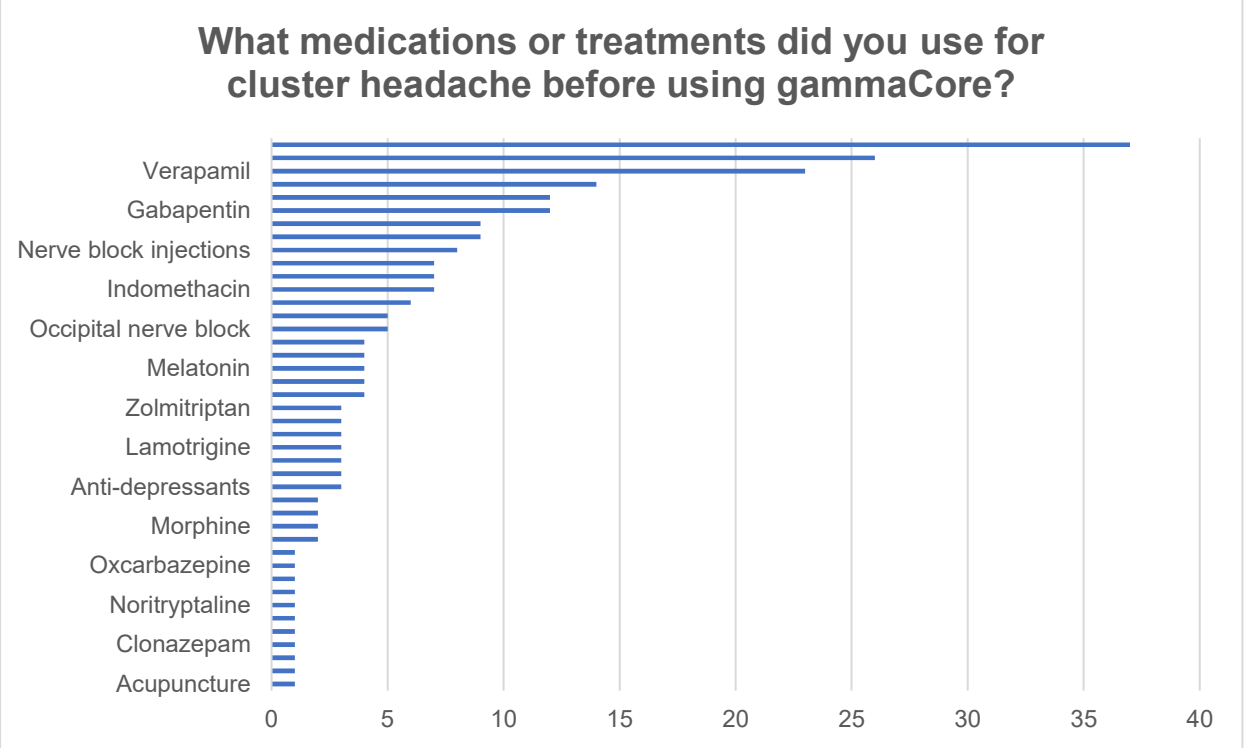
4. Effectiveness of device

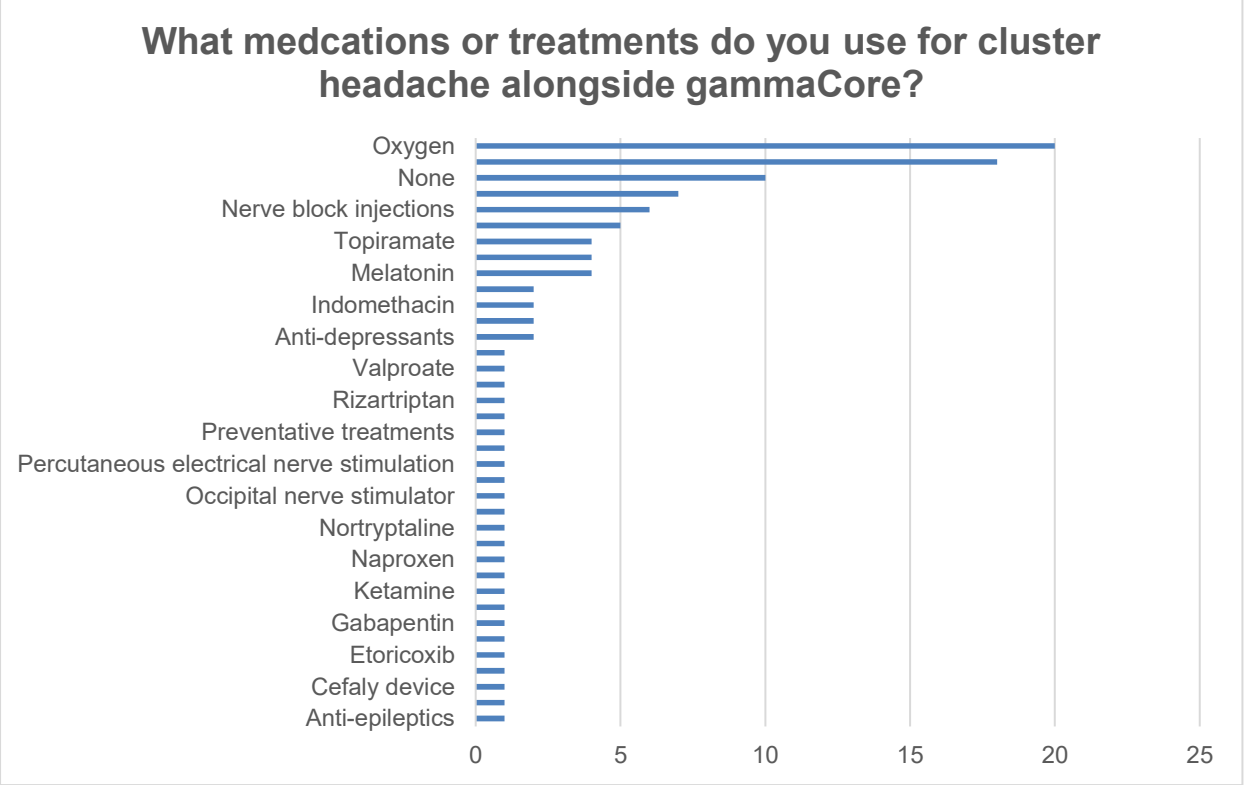
If you use gammaCore to reduce the pain of a headache, how long does it take for the pain to subside?



If you use gammaCore to prevent headaches, has it reduced the frequency or severity of headaches?

5. *Other medications/treatments*





Of the 60 responders that answered both questions, 42 indicated that they had reduced the amount of other medications/treatments they were using since starting treatment with gammaCore.

6. Patient statements

1. Does gammaCore have any positive effects for you, your condition and/or your quality of life? Please consider things such as: your physical symptoms; your ability to perform daily activities; your quality of life, lifestyle and/or social life; your state of mind, emotional health and/or wellbeing; the effect on family, friends and others.

1	I feel zen
2	No
3	I have not noticed any difference.
4	Reduces clusters by 50%
5	80% improvement in physical health Back ground daily headache, reduced from a 5/10 to a 1/10 Pre gammascore was getting up to 14 attacks daily, went down to 4 weekly a month post gamma core use Missed 10 days on average of work a month: post gamma core, reduce this to missing 10 days in 6 months Emotional was a lot happier. Finically had more money, as able to work. Was able to stop traveling with oxygen continuously. Could get our more freely Able to spend more time and family and friends
6	I've been pain free ever since use. I would say I live life as normally as possible.as if I was like someone without clusters. I'm working longer my family life has never been better. If gammacore was lotto then I've won.
7	Tones my cycle down and out
8	I experienced no positive effects in reducing my cluster headaches using gammacore. There were no changes to using it prophylactically or acutely over 6 months. The cost was prohibitive to longer use, given that I hadedications that worked more effectively (sumatriptan). I found the support from the manufacturer lacking, particularly when I fed back the results and asked for advice.
9	All of the above examples
10	It has reduced the frequency of severe attacks but hasn't stopped the attacks,most of them are at a lower level now.I don't feel as low as I was before using it.
11	Yes helps with every thing not pain free but does help reduce intensity and frequency but not all the time, I hoped and got a great boost at first but it reduced a bit through time but still helps to a degree still got positives.

12	Yes very positive as at the moment it has stopped my clusters it's been a year since my last one.
13	Sorry no help what so ever
14	GC has brought my daily pain and cluster attacks to a lesser level. It is cleaner I feel in that although it's an external device I am not inputting drugs into my body. The sensation of the device feels positive to the condition and I can say whilst I have not returned to any full functions I know by having the device at hand I can be ready to deal with an attack so I am less restricted. Socially not that I get out much I get on with GC use and after dealing with myself explain to others what it is, so socially it has become more accepted. It does help to be positive with CCH.
15	I no longer have time off work as it has substantially reduced the severity of my headaches.
16	Although I have only been using gammaCore for a short time I do feel that it is helping to reduce the number of headaches that I get and has reduced the oxygen usage. Any reductions in the number of headaches improves quality of life and state of mind.
17	Reduces the cluster headaches therefore making my quality of life generally more manageable
18	Dont feel i can answer this question as only been on gamma core 1 week
19	it has greatly reduced my most severe attacks,allowing me to have a better lifestyle throughout the day.
20	Yes, it allows me to have more of a normal life and where the pain subsides quicker I don't have 2 hours pain with each attack. This allowed me to consider getting back into work and going out with friends again. I'm definitely happier now I know that something works and I don't just have to wait out the pain.
21	Yes
22	Absolutely, it has reduced the number of headaches by 90%. It has magically changed the way I live, almost headache free. The quality of life change is amazing after suffering daily for almost 30 years.
23	It stops shadows from developing into full-blown attacks, so reduces the overall number of attacks that I have. This has very much helped with my

	mental health, my hobbies and the effect the condition has on my family. I still have attacks, but the number has definitely decreased.
24	Has had no effect at all
25	Gives me a life that I would consider would be how it feels if one was living with out ch
26	Yes, absolutely, I was able to return to work and mange my migraines with GammasCore. Thankfully I have not had an episode of severe migraine and vomiting, and the panic attacks I used to get associated with migraines. I felt suicidal with the pain, it was that severe.
27	Yes hugely positive. I am more active, take part in sports. I am socialable now and feel a lot more confident to drive and get out and about. My physical symptoms are greatly reduced which has reduced the level'of pain, number of attacks and my well being all round. All my family and friends have commented on how much better and happier I have been since I started the treatment. I am less grumpy and irritated because I am in less pain.
28	I feel gamma core has reduced the intensity of my headaches. I still have headaches every single day but the pain scale has reduced. This has a massive impact on my well being as I am able to participate in physical activity more. I preform better at my job. I enjoy social events more.
29	Yes use gammacore instead of injecting myself.
30	Yes to all the above.
31	Yes I'm able to carry on my life as normal because even though I still have the headaches the severity of pain is now tolerable and unless you know the symptoms you wouldn't be aware I was having one. The pain scale has gone from a 10 down to a 3.
32	None
33	Yes I don't to get many cluster headache.
34	I consider GammaCore helps keep my Hemicrania continua at low to moderate pain levels. 95% of time I can carry out normal activities but I have constant headache pain in waling hours, ie 24/7 a headache This affects my wellbeing significantly, making me bad tempered, intolerant to noise & stress.

35	Without out it, I would have given up as I became Chronic with clusters every day starting Jan 2010 (used to be Episodic) - only the gammacore brought the number of attacks a day (8-10) down (to 3) and the severity of the pain down to a manageable level. It meant I was able to manage some sort of life, see my family and friends and cope with my other health problems (Ihave SUNCT & chronic migraine aswell as insomnia & sleep apnoae as most of my clusters are at night). It is so much more convenient than oxygen to incorporate into daily life and less threatening to other people.
36	Still having regular cluster headaches and migraines, not much difference at present but only started machines recently
37	All of the above
38	Avoiding verapamil and prednisolone with their unpleasant side effects and potential risks has made me feel better about my condition and has had a good effect overall in my quality of life and wellbeing.
39	All of thecabove
40	gammaCore is as essential to my life as levothyroxine is. Before the device, I would have 4+ attacks in a CH day I would have about 16-20 days a month with attacks . I lost my job, my ability to perform everyday tasks such as cooking or cleaning, my ability to drive a vehicle (as there were 12 time slots in a day that an attack may occur, and I became highly photosensitive), my ability to exercise at any pace, and it put great strain on personal relationships. I stopped going out and seeing other people (as on days without headache there was a lot to catch up on). The financial strain was intense. Many attacks had me feeling suicidal, both due to the sheer torture and due to everything that I'd lost to the condition. It left my family feeling helpless and confused (if they understood what I was going through) or pushing "alternative medicine" at me (I soon avoided talking with them as it made me want to yell at them) or prompted them into telling me to stop being lazy/that I just needed to move on with life. Socially it was very isolating. To my husband it was a great deal of stress and strain and he developed anxiety. I missed most social events, dinners, birthdays, holidays, and was usually trapped in the house with all light blocked out. Sleeping became difficult due to panic attacks I'd get before bed. gammaCore has reduced my CH attacks from 4-6 per day for up to 20 days each month (80-120 excruciatingly severe attacks per month) to an absolute maximum of 4 attacks total in a month. Usually it is only 1-2 mild-moderate attacks on one day. I'm attending university again to retrain for a job that accommodates my condition better. I usually feel able to tend the garden,

	do routine housework, cook food and I've recently returned from a research trip abroad for my MSc. I still do not drive as the photosensitivity has remained enough to make me feel unsafe, but I can take public transportation now. I'm able to attend most social functions now and have a high attendance rate at university. Since I'm able to get out and about I have more money to take care of basic needs, and more motivation for enduring pain (and the negative mood associated with attacks) when it does strike. As I'm able to excerise up to a moderate level now, my muscle and joint pain has gone away and I sleep better. I don't get nightly panic attacks and my husband also has had his mental health significantly improve. Physically the attacks are far, far fewer and typically sit at the lower end of the pain scale whereas before they were always so high at the top that suicide seemed a reasonable way to make the pain stop. gammaCore doesn't leave me with any side effects, unlike pharmaceuticals which at worst made me collapse and at best made me feel extremely depressed and physically ill.
41	seem to sleep better Too early to say hoping to be able to cut down tablets
42	No physical symptoms with gamma core only with other medications. No problem with daily activities unless I have a cluster coming on. My quality of life is much better. My well-being is a lot better my mind is not perfect but much better. My family can now approach and except me.
43	I'm some 75% better than I used to be before the gamma core
44	All of the above, yeah
45	Yes! A HUGE improvement in my quality of life, which impacts on the life of my husband, three children, elderly mother, wider family, and friends. I had become anxious about leaving home, because of the massive embarrassment of having an attack in public, and rarely did so. I now hardly think about this aspect of cluster headaches/paroxysmal hemicrania. I feel so much more positive and lead an almost normal life again. My attacks have become tiresome rather than life changing in the worst way.
46	Mainly the recovery time in between Where as before I would be unable to do much at all in between the attacks now I am able to do more
47	Very big difference. Acts like a kind of buffer. The severity of the flares is generally less than before, the frequency is much less than before and the duration of a flare, which could have been weeks before Gammacore, is generally reduced to maybe a day sometimes a bit more. It therefore has made a dramatic improvement in my quality of life all round.

48	Not been using it long enough really yet.
49	Effect has definitely been positive. Have gone from having cluster headaches, at one point 19 in a 21 day period, to having only had 3 migraine headaches in the four or so years I have been using gammaCore.
50	A very positive effect. It reduces number of migraine attacks but mostly it reduces the intensity of pain. It allows me to perform better than previously when I have a migraine and has therefore significantly reduced the number of days that I am unable to leave the house as a result of migraine. I can take part in more social activities and sign up to courses and commit to dates whereas before I wouldn't due to the likelihood of having to cancel. I no longer (or rarely) have several consecutive days of severe head pain. This used to impact negatively on my mood at times. In addition I take less medication for migraine attacks as they are less severe. This means that I am less likely to feel tired as a side effect from them. In addition I feel that it is more healthy to be able to reduce the amount of painkillers I take. Also holidays are easier. I am less likely to have such a bad migraine that I miss out on quality time with my husband, family and friends. I also feel that I am able to have a normal life without always having to back out of events, be unable to do activities etc and also feel that I am a more useful person as result. I think that my husband would agree that it has been a positive treatment for our life together too.
51	Great improvement in quality of life!
52	Yes, I am able to complete more daily tasks and I feel more positive mentally. I am able to social more as the frequency of cluster heads have reduced. For the last few months i have had no cluster heads.
53	Physical symptoms , Quality of life, emotional health, effect on family friends
54	Gammacore has been fantastic for me. Aside from slight facial distortion during use, it is a fast and effective treatment which avoid taking an form of drug medication. I found it didn’t worth immediately for me so I was doing it three times a day for two minutes but also using sumatriptan injections when attacks came on. After about two weeks of regularly Gammacore treatments my headaches stopped (with the exception of just one or two). The treatment is pain free, non invasive and I have no lasting die effects after use meaning I can use it throughout the day at work or with friends. I am between bouts at the moment but would definitely want to use this treatment again when my cluster headaches inevitably reoccur.
55	Nothing so far

56	No longer suffee any symptoms. Social life is better. Work is better - no sickness and aa a result i have succesfully applied for jobs. My state of mind is immeasurably better and im able to exercise and be fitter.
57	all of the above
58	Since using gammaCore my life has changed so much. I am able to do normal daily duties such as cleaning, washing, cooking, as well as being able to work full time. Previously it was affecting work so much that I was put through a formal process due to the amount of time I was off sick.This only added extra stress and made me feel completely helpless and hopeless against something I had no control over. I can now go out without having to worry if I am going to have an attack and I am no longer having to carry my oxygen around with me. When family and friends now make arrangements to meet, I now look forward to it. I no longer worry that I might have to cancel at the very last minute, or worry about how they will react if they see me in a full blown attack. My concentration and energy levels have returned as has my sense of humour, which has been noticed by family, friends and even work colleagues. People who have known me for years, well before I started with Clusters, have commented "there you are! We've missed you, welcome back" To put it bluntly, I have my life back!
59	no positive effects. i am a chronic cluster sufferer.

2. Does gammaCore have any negative effects for you, your condition and/or your quality of life? Please consider things such as: your physical symptoms; your ability to perform daily activities; your quality of life, lifestyle and/or social life; your state of mind, emotional health and/or wellbeing; the effect on family, friends and others.

1	No negative effects
2	No
3	Not noticed any side effects
4	Acceptance in general society
5	No negative effect. Don’t like using in public, as people look. But with 3 times a day use, chances are it only needs to be done once in public if I’m out for the day. But less annoying then portable oxygen and people looking
6	None

7	Gave me facial pain after cycle had ended...neuralgia type pain which still occasionally appears now 3 years after last cycle
8	I found the device a bind to use, especially at work or in public. I did find that it would make me feel nauseous, most often toward the end of the day.
9	None
10	There are no negative effects to report.
11	No.
12	No negative effects
13	No negative effects
14	There is the sensation, the drag but that's the treatment and that is nothing to the the condition so you cannot list this as 'negative'. GC works for me.
15	Recently I was without the Gamma Care as my previous device had run out my headaches got a lot worse & the frequency increased.
16	It has no negative effects.
17	No
18	None as yet
19	My neck can spasm quite a lot when I use GammaCore when an attack is especially bad
20	No
21	It has no negative effects at all. Like taking any medication, I have to remember to use the gamma core every morning when wakening then again in the evening before sleeping.
22	No- I just need to remember to take it with me when I am out.
23	As above
24	None
25	No. I only wish that the GammaCore device would be sent out without having to make requests. I am literally panicking if I have run out and am waiting for a new top u card to arrive. Previous to the card, I was waiting for the device to arrive. This is through no fault of the the providers - but down

	to me not notifying / making requests on time. When I have requested the top up card, it ids delivery imminently.
26	No none at all.
27	None
28	I didn’t find it effective and was unsure if it temporarily worsened my symptoms. I began to use it whilst I was already 2 months into a cycle and continued for a few weeks but found no benefit. I was hoping it would be better as a non-invasive treatment but I did not think it suited my needs and provided no easing of pain.
29	No
30	No noticeable negative effects
31	It does sometimes make your throat a little dry/hoarse but I've never had any negative experiences - I don't think I could cope without it's positive effect on the pain levels I have to cope with. The effeciveness on reducing the pain between using it and O2 is obvious
32	None
33	No
34	Not at all.
35	Sometimes hard to find a place to use it away from the public
36	gammaCore has no negative effects on me or my life. It is the only treatment that does this for me.
37	Setting the side time to do treatment . Cannot do lunch time treatment as can be out or at work.
38	I feel tired after using the gamma core Some activities are affected Quality of life is much better State of mind again much better my health as improved and so as my wellbeing My family are more at ease with me now.
39	I don't sleep well, but not sure if that's related to the gamma core or not
40	None
41	No

42	No,
43	None
44	None that i know.
45	Obviously preferred it when the cost of the device was met by the NHS. I am currently paying £1000 per annum to use the device but now I am dependant on it, I don' t feel I have any choice but to continue.
46	Not really. I have to remember to take it when I'm away and sometimes its a bit time consuming to treat regularly but I know that if I do reduce the number of treatments that I give myself then I will start getting more severe headaches again. Thus it is something that is worth the very little effort required.
47	None whatsoever!
48	No
49	None what so ever, for me it has been a revelation helping me with my cluster headaches.
50	Apart from the face distortion during use I have no negative side effects and even this is a small price to pay for a very effective treatment.
51	Nothing so far
52	No negatives
53	none
54	Absolutely none at all, apart from my friends laughing at me when my face starts to distort when using it, but that's what friends are for, to make light out of the situation
55	no

3. Would you recommend gammaCore to another person with your condition? **57 (95%) Yes, 3 (5%) No.** Please explain your answer.

1	Yes	

2	No	It didn't work for me. I tried a few different positions and angles, and confirmed with the gammaCore representative but nothing I did made a diffrerence
3	Yes	Its worth a try as ive spoke to people it has worked for and i would prefer this over tablets.
4	Yes	Each individual is different and not all treatments available are suitable but if gamma core can reduce the amount of pain or episodes then I would recommend it.
5	Yes	Yes. It gave me 80% improvement, with no side effects and managed to get off some of the medication I was taking
6	Yes	It has no side effects it's none invasive. It can change your life and easy to use
7	Yes	It made my cycle end after 2 weeks use paired with keeping my hydration at maximum...5 to 8 pints a day filtered room temp water...both together worked best...he water helped the gammacore do its thing better for sure Needs to be made so that it can just be rechargeable via USB without any having to pay an extra charge to unlock more usage...that's just cruel as cluster headache people are usually out of work and cant afford to be doing that Take note as many cluster headache people have said this including myself
8	Yes	only because anything is worth a try and may work well for others, it did not help me
9	Yes	It didn't work for me, but I wouldn't say that I wouldn't work for others. On that basis yes, I would say try it. But it is cost prohibitive if the effects are slight.
10	Yes	Can. E effective without medication related side effects
11	Yes	It has lowered the pain level of a lot of my attacks,Instead of 3 or more severe attacks a day I now get about 3 a week that are severe all the other attacks much lower.
12	Yes	Any thing that helps with the pain for the condition is a god send, has definitely help me in all ways
13	Yes	
14	Yes	May work for uher people worth trying anything what may help

15	Yes	It allows an option to deal with the conditionthere and then. It is a device that fits in your pocket and when an attack strikes you are able to remove yourself and deal with this. Day to day treatment with the device has reduced severity so this is all positives.
16	Yes	It is more effective than prescibed medication whilst it is not a complete cure it does make a substantial improvement.
17	Yes	Any thing that can help a person is well worth trying.
18	Yes	When you suffer with this condition anything which could reduce it is worth trying. This has no side effects and does not involve taking medication which effects the whole body. A superb invention one which I whole heartedly endorse.
19	Yes	Really helpful for migraine..
20	Yes	before i tried gammacore i was at the end of my tether with my condition..although i still need other medication gammacore is another link in the chain which is helping to manage my condition.
21	Yes	It has helped me so much and if it can help someone else the same that would be amazing! And also where it’s not a drug there isn’t anymore substances going into your body so it’s better from that point of view as well.
22	Yes	
23	Yes	It has been unbelievable for myself, but I realise it may not work for everyone.
24	Yes	It has been so helpful, and is definitely one of, if not THE, best treatments for chronic cluster headaches around. I have been through three neurologists' 'arsenal' of medications, and nothing has helped as much as the gammaCore device has. Sometimes I need help to get to it and set it up at the onset of a quick-starting attack, but aside from that, it is so easy to use, painless, has no side effects (unlike medications), and is easy to carry around. It is definitely the best treatment that I have come across and I count myself as extremely fortunate to have been able to access this treatment.
25	No	The device had absolutely no positive effect on my condition at all
26	Yes	Of it works for me with amazing results then surely a no brainer for anyone else

27	Yes	Yes, absolutely, there are no side affects to using gammaCore.
28	Yes	As there are no side effects for me, I feel it is something far less harmful and invasive to try than many other treatments available. It's also very portable and easy to use.
29	Yes	It has reduced my intensity and pain level. I hope if I am able to continue using this device maybe I will have a headache free day for the first time in 5.5 years
30	Yes	Helped the management of my pain. Been able to reduce the amount of injections I take.
31	Yes	100% because it works
32	Yes	
33	Yes	Although I did not find it helpful, I have heard it is beneficial for some people so it is worth them trying it.
34	Yes	I know it's not for everyone but it seems to work for me it's the best thing I have ever had for my headaches.
35	Yes	Always worth a trial, but cannot predict how effective
36	Yes	see my last answer
37	Yes	Simple and easy to use, no side effects
38	Yes	It's not nice to use though and almost mpossible when treating a headache. It only suits me for preventative use
39	Yes	Although I have not benefitted from using gammaCore acutely, I found it effective in reducing the duration and frequency of attacks in my last bout. It could be that other patients with episodic CH like me will find it equally effective for prevention, and hopefully in the acute attacks as well. Most importantly, it reduces the need for steroids and high doses of verapamil avoiding a number of common side effects (dizziness, tiredness, constipation, bradycardia, peripheral oedema).
40	Yes	No side effects and no drugs !
41	Yes	I know that for me gammaCore has been a miracle device (the percentage decline in attacks a month is greater than 95%, which is phenomenal). It may not be as effective on others as it is on me, but even if it had reduced everything "only" by half then it would have still

		been amazing. It's given me the ability to live a relatively normal life again. If it wasn't for gammaCore we wouldn't have decided to have children. With a condition as painful and disruptive as CH there's an ethical duty to attempt everything reasonable to improve the condition and improve quality of life.
42	Yes	I did try earlier form of machine which I found did not help situation. I think everyone should try this as different treatments help different people. My one worry is would you have to use the machine for ever.
43	Yes	If they have felt so isolated for years like me with pain and depression because of my clusters and trying other types of remedies and drugs plus being hospitalised for weeks I would say yes to trying the Gamma Core it as been a life saver for me.
44	Yes	It's much better than been pumped full of medicine which can have adverse side effects, it's a quick and effective treatment for my headache
45	Yes	Mental wellbeing, not living in fear, enjoying life not dreading missing important family gathering because of migraine, being able to go to work and function
46	Yes	Firstly, it is always good to have something new to try. Secondly, and most importantly, it has transformed my life and could very well transform the life of another cluster headache survivor. It also helps with my other headache conditions - primary stabbing headache and migraine with and without aura.
47	Yes	It makes you feel you are trying something positive It is non drug related which is a big plus Though regularity of use must be emphasized
48	Yes	I know through a hemicranea continua group of patients that a lot of us with this condition are benefitting from Gammacore.
49	Yes	
50	Yes	My experience with gammaCore has been so positive, I have already recommended it to several people.
51	Yes	I think it will likely reduce the severity of their migraine attacks. It will start to be effective within a few weeks. Should it not be beneficial then it will not had any adverse effect. Another point is that prior to GammaCore I had tried many different drugs to see if they would

		help. These included anti-depressants, anti-schizophrenic drugs and other beta blockers. Some of these drugs had very unpleasant side effects and most were ineffective. The dose was always being increased to see if they were more effective at a higher dose but then side effects became more and more unpleasant. Eventually the side effects and the feeling of causing harm to my body, usually in the absence of any significant improvement, would mean that I had to stop. The GammaCore therapy does not have any of these side effects.
52	Yes	No side effects whatsoever, just potential benefits. This is so different to numerous medications tried, all of which had side effects which I persevered with hoping for relief which unfortunately never materialised
53	Yes	Because it has redcued my cluster heads within two months since using gammacore
54	Yes	I have tried and tested all other medications available to no avail. Gamma Core has been a life saver for me, and i am sure it would help other suffers as well.
55	Yes	It is effective, easy to use, non-invasive and subtle. A truly great treatment which enables me To get on with my life having suffered from such painful headaches for over 10 years now.
56	No	I havenf saw any benefit whatsoever
57	Yes	Quite simply its transformed my life, removing all the worry and suffering.
58	Yes	It helps reduce the severity of the headaches. (had to do my best to understand handwriting)
59	Yes	As I mentioned earlier, this device has been a complete game changer for me. Considering what I was going through, I would never have believed anyone if they had said this little device will stop cluster headache shadows and attacks as everything else had failed. In fact, when my consultant suggested it, I did not give it much hope in working, but I just cant explain just how glad I am that he convinced me to give it a go. For everyone who has this debilitating condition, all we want is relief, for the pain to go away permanently, but to be honest, we will even take a few hours being pain free. The gammaCore can do this for people. OK it may not be 100% effective for all sufferers, but when you are desperate, you will try anything,

		praying for any form of relief. This little handheld device literally could be a life saver from "suicide headaches"
60	Yes	only to help with mild to moderate pain

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

NICE Medical Technologies Advisory Committee

gammaCore

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	The Migraine Trust
Contact person's name	.Mr Angus Baldwin
Role or job title	CEO
Email	
Telephone	
Organisation type	Patient/carer organisation (e.g. a registered charity) ☒ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☒ Education ☐ Campaigning ☒ Service provider ☐ Research ☒ Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? The Migraine Trust is not a membership organisation	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

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If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

Sufferers and healthcare professionals

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Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

The impact on the lives and needs of Cluster Headache (CH), sufferers often go unrecognised and untreated. Frequent, disabling cluster attacks can be devastating to the sufferer. Sufferers will typically be woken several times at night with severe excrutiating pain, as well as have their days interupted by attacks. This willl affect their quality of life and ability to function in work and contribute to regular activities.

People with cluster headache can feel socially isolated and may be viewed as unreliable by others (for example employers), who do not understand the debilitating effects of the condition. Furthermore, the existing treatment options are very limited and some patients find these either intolerable or ineffective. Hence the availability of this therapy could have a positive impact on the lives of many cluster headache sufferers.

CH is generally considered to be the most painful medical condition known to mankind and most female sufferers describe the pain as being worse than childbirth (OUCH UK).

2. How do symptoms and/or the condition or disease affect carers and family?

CH impacts on all aspects of a sufferer's life and by its unpredictable nature. Hence many sufferers have lost their jobs, or at least had to change jobs because of their CH. Typically, they will be woken several times at night with excrutiating pain and this impacts on their ability to function and participate in family activities and impacts on their relationships.

3. Are there groups of people that have particular issues in managing their condition?

As with all treatments, not everyone can derive benefit or find the existing treatments tolerable or appropriate. Hence there are sufferrers who have yet to find an appropriate treatment for this devastating condition. For example, side effects limit therapeutic dose escalations of the preventive Verapamil, and cardiovascular conditions are a contraindication to Sumatriptan injections for acute treatment. These patients could rather be offered Gammacore for both abortive and preventive treatment.

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Experiences with currently available technologies

4. How well do currently available technologies work?

Not everyone benefits from the current treatments due to intolerable side effects or they may be ineffective. A non-drug treatment such as gammacore will be better tolerated and is portable for treatment as needed, without cognitive impact on the ability to function at work or daily activities.

5. Are there groups of people that have particular issues using the currently available technologies?

Patients with contraindications to standard treatments (examples in 3. above), will be left without a treatment option and their suffering would be intolerable whihch is ethically challenging to ignore.

About the medical technology being assessed

6. For those with experience of this technology, what difference did it make to their lives?

We understand that gammacore has offered a safe, effective self-treatment option that has enabled many to remain independent and optimised their ability to function, both throught acute and preventive treatment.

7. For those without experience of the technology being assessed, what are the expectations of using it?

To reduce the overall number of attacks experienced and/or the severity. Acutely, it may abort the cluster attack with early treamtent, which offers the potential to improve quality of life and reduce suffering.

8. Which groups of people might benefit most from this technology?

Cluster headache sufferers.

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Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

Key messages

10. In up to five statements, please list the most important points of your submission.

- New treatment options with fewer side effects are needed
- Cluster headache has limited treatment options
- The pain is severe and debilitating and requires effective treatment
- It is unethical to withold a safe and potentially effective treament for a condition of suicidal pain
- the impact on quality of life, socioeconomic and family input can be enhanced.

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including Diagnostics Assessment) and will be held on the Institute's databases for future reference in line with our privacy notice.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

NICE Medical Technologies Advisory Committee

gammaCore

Please read the guide to completing a submission fully before completing this template.

Information about your organisation	
Organisation name	OUCH (UK)
Contact person's name	Scott Bruce
Role or job title	Trustee
Email	
Telephone	
Organisation type	Patient/carer organisation (e.g. a registered charity) ☒ Informal self-help group ☐ Unincorporated organisation ☐ Other, please state:
Organisation purpose (tick all that apply)	Advocacy ☒ Education ☒ Campaigning ☒ Service provider ☐ Research ☐ Other, please specify:
What is the membership of your organisation (number and type of members, region that your organisation represents, demographics, etc)? 4000 active UK Sufferers or Supporters with a cascade reach of around 50,000 sufferers worldwide	

Please note, all submissions will be published on the NICE website alongside all evidence the committee reviewed. Identifiable information will be redacted.

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

If you haven't already, please register as a stakeholder by completing the stakeholder registration form and returning it to medtech@nice.org.uk

Further information about registering as a stakeholder is available on the NICE website.

Did you know NICE meetings are held in public? You can register on the NICE website to attend a meeting up to 20 working days before it takes place. Registration will usually close 10 days before the meeting takes place. Up to 20 places will be available, depending on the size of the venue. Where meetings are oversubscribed NICE may need to limit the number of places we can offer.

Sources of information

What is the source of the information about patients' and carers' experiences and needs that are presented in this submission?

First Hand and Second Had submissions of patients using the device

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

Impact of the symptoms, condition or disease

1. How do symptoms and/or the condition or disease affect people's lives or experiences?

Cluster Headache is an excrutiating pain condition, that is known as one of the worst pains in the world. sufferers lives are destroyed by the pain and attacks.Sufferers often loose their livelyhoods to the condition.

2. How do symptoms and/or the condition or disease affect carers and family?

Cluster Headaches has a whole family condition, in that the sufferer will find themselves isolated as the pain is not one that others can help with, which in turn affects the familiy and friends as lives are disrupted loss of income becomes a sizable factor in the breakup and disruction that this desease causes.

3. Are there groups of people that have particular issues in managing their condition?

yes, regional specialism and lack of awareness of the condition impacts sufferers ability to access the correct treatments

Experiences with currently available technologies

4. How well do currently available technologies work?

currently there is no technology on the market that is 100% reliable in the treatment of this condition. current technologies are all in the research stages with non approved for use in Cluster Headache Management. So special funding is required. all current technology treatments are invasive surgical procedures.

5. Are there groups of people that have particular issues using the currently available technologies?

All sufferers must cycle through a significant number of pharmalogical treatments to gain access to surgey to allow them to have a life where the pain is less than they currently experience. because of this step process in care, on average 5 UK sufferers end their lives due to the pain per year.

About the medical technology being assessed

6. For those <u>with</u> experience of this technology, what difference did it make to their lives?

Patients using the Device who have had success with it find their lives imeasurably better than when they had no treatment plan or been down the road of various other treatment plans.

They feel it makes a valuable difference and many say it saved their lives.

Many feel that is a low side effect low risk treatment for their headaches.

7. For those <u>without</u> experience of the technology being assessed, what are the expectations of using it?

That is non pharmological solution giving them limited to no side effects that the current on-lable and off label treatments have on their bodies.

It is a solution short of surgery and the risks that internal modulation would do.

8. Which groups of people might benefit most from this technology?

Many groups of sufferers would benefit. those who don't respond well to traditional treatments but who don't want life changing surgery.

Episodic sufferers who need to wait 4-6 weeks to see a neurologist when a bout returns if they have a Gammacore device it can be charged and ready to use on the first attack.

Additional information

9. Please include any additional information you believe would be helpful in assessing the value of the medical technology (for example ethical or social issues, and/or socio-economic considerations)

National Institute for Health and Care Excellence
Patient Organisation Submissions for Medical Technologies - Submission Template

Cluster Headache sufferers require high cost treatemets or surgey Oxygen and Gammacore can be used as accute abortive treatment cost effectively.
Gammacore has also seen benefits of preventative treatments in some sufferers.

Key messages

10. In up to five statements, please list the most important points of your submission.

- Gammacore is an easy to use solution
- for those it benefits it changes their lives positively
- it avoids brain surgery
- it has few if any side effects
- it can be used accutely and preventatively

Thank you for your time. Please return your completed submission to medtech@nice.org.uk

Using your personal information: The personal data submitted on this form will be used by the National Institute for Health and Care Excellence for work on Medical Technologies (including Diagnostics Assessment) and will be held on the Institute's databases for future reference in line with our privacy notice.

National Institute for Health and Care Excellence

External Assessment Centre correspondence table

MT323 GammaCore for Cluster Headaches

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission section #	Question / Request	Response	Action / Impact / Other comments
Company Reps			
Section 7.6 (table B21)	Please provide some clarity on where the figures in this table were obtained	Detailed response from the company representative received	
	confirm that all of the data used for resource use in the scenarios is from unpublished post-hoc analysis from the PREVA study.	Some but not all of the resource use in the model is from unpublished post-hoc analysis, depending on the scenario selected: • The resource use data for gammaCore responders is from a post-hoc analysis, apart from one of the response definition scenarios "50% using means" which uses published resource use (Gaul et al) from all patients randomised to the gammaCore arm. • The resource use for gammaCore non-responders in the first 3 months (while still on gammaCore) is from a post-hoc analysis, apart from one of the response definition scenarios "50% using means", which uses published resource use (Gaul et al) from all patients randomised to the SoC arm. • The resource use for gammaCore non-responders after 3 months (who discontinued gammaCore) uses published resource use (Gaul et al) from all patients randomised to the	

		SoC arm. The exception is the scenario "gammaCore non-responder use from PREVA", which is obtained from the post-hoc analysis (non-responders' actual baseline values). • The resource use for SoC uses published resource use (Gaul et al.) from all patients randomised to the SoC arm.	
	• **highlight any other data that is from unpublished sources.**	The only other HRU assumption that is not explicitly published is the proportion of patients taking nasal vs. s.c. sumatriptan. This was from the Marin study, for which we had the patient-level data. Although the Marin study is published they do not explicitly state what proportion of sumatriptan users were on the nasal formulation.	
	• **give any further information about the origin of the survival analysis numbers reported**		
	• **clarify the costing model for the recharge card – does it expire after a fixed time, a certain number of uses, a combination of these, or something else?**	The refill card activates the gammaCore Sapphire device so that it is able to deliver 93 consecutive days of nVNS therapy. On each of the 93 days, a patient can use a maximum of 30 stimulations within that 24 hour period. After 24 hours, another 30 doses will become available.	
	Is the gel replaced together with the recharge card at the same cost, or is it an additional purchase?	The gel is replaced along with the refill card. There is no additional cost, and if patients require extra gel for any reason, we will send free of charge.	

	Please could an additional questions? We have identified an abstract and poster: *Jenks, M. et al. 2016. A preliminary cost-utility analysis of non-invasive vagus nerve stimulation therapy in patients suffering with headache and functional disorder multi-morbidity. Value in Health 19(7), p. A698.* The data for this model comes from an NHS cohort study that I believe is reported in the poster: *Strickland I et al.* ***Non -Invasive Vagus Nerve Stimulation As A Treatment For Headache Patients With Multi Morbidity: Real World Experience In English Primary Care.*** *ISPOR 19th Annual European Congress Vienna, Austria October 29 – November 2, 2016* And then later reported in the publication: *Strickland I et al.* ***Noninvasive Vagus Nerve Stimulation in a Primary Care Setting: Effects on Quality of Life and Utilization Measures in Multimorbidity Patients With or Without Primary Headache*** *Am J Manag Care. 2018;24:S517-S526* I noted that the cost model includes prescriptions, with 3.81 prescriptions per person per month in the nVNS+Standard care arm and 3.65 in the standard care alone arm. Prescriptions are costed at £8.25. These figures aren't reported on either of the publications above, are you able to give any further information about what they included and how they were costed?	You are correct in the fact that the cost-utility analysis conducted by YHEC and presented as an abstract by Michelle Jenks is based on data reported in the multi-morbidity study conducted in primary care and authored by myself. I have attached the relevant publications in case you do not have them. <MUS Clinical_HCR data.pdf> <YHEC FINAL.pdf> <Strickland 2018.pdf> I should make it clear that this cohort of patients were defined as having a primary headache diagnosis (nearly all were migraine or medication overuse headache) plus two other commonly associated co-morbidities. These patients were not Cluster Headache patients and are very different to the population criteria being evaluated by NICE. During this evaluation we interrogated primary care data records to examine changes in various indicators of "healthcare resource utilisation" with prescriptions being one of those metrics. Where data was available we took a time-matched period, pre- and post-gammaCore for each patient to see if the use of gammaCore changed other medications being prescribed. I hope this helps your understanding, but again I would reiterate that I don't believe	

		that these publications are directly relevant to the MTG patient scope.	
	Thank you for responding so quickly. James Morris has kindly already responded to me regarding the differences between the UK and German perspectives in the published model. There were another couple of questions concerning the PREVA data, but related to the submitted model, and the Gaul paper. In the submitted model the number of patients used for the gammaCore arm resource use is 35. 1. Am I right that these are the ITT patients who are randomised to SOC+ nVNS and also have resource use data available for the last fortnight of the randomised phase? 2. Could you clarify why there are 35 in this group, but 32 presented in the Gaul 2016 paper (figure 4a, abortive medication use)? 3. In the Gaul 2016 paper there is a statement in the discussion that "Only patients with chronic, treatment-refractory CH were included because of their stable CH attack frequency and intensity.". We could not find anything in the stated inclusion criteria that led to this conclusion, are you able to add any additional insights?	**1.**Yes. We have n=35 patients for which we have matched data (attack frequency and resource use) available from both the randomised phase and the open label phase of the PREVA study. 35 is the validated number and all of the data for the model was produced and validated by an independent statistician **2.** The 32 that is mentioned in the Gaul paper was based on the Full Analysis Set, as defined in the study protocol, and included subjects who provided complete, matched data, for the outcome measure of attack frequency. The original statistical team did not provide complete SAS Programming and we were unable to directly match the 32 through the parameters we tested so used the validated 35 figure on our model for your review. As we did not identify any significant outliers in the data, we believe the data, while not identical to that presented in figure 4 of Gaul et al.,, offers the same insights. **3.** See table 1 (page 538) of the Gaul paper: This shows patients with CH for close to 5 years, and current meds. This portrays the stability of the patients which is in keeping with the cCH population. I have included the full inclusion criteria for	

		the study below: Full details were not published in the paper due to space constraints. **Inclusion Criteria** The subjects had to meet all of the following criteria to be eligible to enter the investigation: 1. Signed Informed Consent Form 2. Subjects between the age of 18-70, both genders 3. Subjects diagnosed with cluster headache for at least 1 year, without remission periods or with remission periods lasting <1 month, in accordance with the ICHD-II classification criteria (2ndEd): a. At least 5 attacks fulfilling the following criteria: i. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated ii. Headache is accompanied by at least 1 of the following: 1. Ipsilateral conjunctival injection and/or lacrimation	

		2. Ipsilateral nasal congestion and/or rhinorrhoea 3. Ipsilateral eyelid oedema 4. Ipsilateral forehead and facial sweating 5. Ipsilateral miosis and/or ptosis 6. A sense of restlessness or agitation iii. Attacks have a frequency from 1 every other day to 8 per day and are not attributed to another disorder iv. Attacks recur over > 1 year without remission periods or with remission periods lasting < 1 month 4. Had minimum mean attack frequency of 4 CH attacks per week 5. Was able to distinguish CH from other headaches (i.e. tension-type headaches) 6. Was capable of completing headache pain self-assessments 7. Agreed to use the gammaCore® device as intended and follow all of the requirements of the study, including follow-up visit requirements 8. Was willing to keep all concomitant	

		medication stable during the entire study period 9. Women of child-bearing potential used 2 methods of contraceptive i.e. hormones and condom	
Authors			
M.Jenks	1. Was there any additional information either published, or as a report that can readily be made available either publically or academic / commercial in confidence? 2. Are differences between the abstract and poster results due to updating the model in the intervening time period, with the poster as the final version? 3. I note that there are significant set-up costs for gammaCore in the sensitivity analysis, could you explain what is included in these and what the base case value used was? 4. Did all the items in table 1 (below) with references as NHS cohort study come from the 2016 poster by Strickland? 5. Are you able to explain further what was included in the prescription resource use, and in the costing for these?	1. I'm afraid not. The only outputs from this work were the model that we developed, the ISPOR poster and a user guide. The user guide explains health economics concepts and how to navigate through the model, rather than providing any technical information (hence probably doesn't give the information that you need). I'm not sure if the model we developed is the same one (or similar) to that the company have submitted either. Both the YHEC model and user guide are now property of ElectroCore, so they would need to provide those documents. 2. Yes, that's correct. 3. A value of £21,606 set up cost was used in the base case. This set up cost comprises a clinic attendance for each person who may use gammCore. This was to account for the fact that based on the early data that we had at the time, for every 1 person who used gammaCore, 1.9	

		people attended an initial clinical appointment (nurse consultation) to discuss the potential use of gammaCore. We included this as it was an additional resource in the clinical data that wasn't captured elsewhere and wouldn't have occurred without gammaCore. The £21,606 value is based on 1,000 patients and is derived from 1.9*1000*£11.37 (cost of nurse appointment). 4. These values were derived from an analysis of individual patient data from the NHS cohort study that we did to populate the model. Hence, they are likely not all included in the poster by Strickland. 5. The cost of the prescription was based on the average cost of a prescription as measure in the individual patient data from the NHS cohort study. Likewise, the number of prescriptions per patient per month was also taken from an analysis of this data. We weren't provided with a breakdown of the type of prescriptions (I don't think that level of information was available) hence whether these are direct or indirect costs.	
J. Morris	As you may already be aware, Cedar have been asked by NICE to provide the external assessment report for GID-MT523 gammaCore for Cluster Headaches. We are currently reviewing the submitted economic evidence and would be very grateful if you could give some additional information on your paper:	The UK perspective described in the published article differed only in two respects from the German model perspective. Firstly, the UK tariff was used to derive utility values from the EQ5D data collected in the PREVA study. Secondly, UK unit costs were applied to resource use data collected in the trial. Beyond these two	

	Morris, J. et al. 2016. Cost-effectiveness analysis of non-invasive vagus nerve stimulation for the treatment of chronic cluster headache. Journal of Headache & Pain 17, p. 43. In this paper there is a result reported for an additional analysis from a UK perspective. Are you able to share any information on what changes were made to the model in order to give a UK perspective? For example, were there any structural or resource use changes, or were changes restricted to costs?	aspects, there were no structural or other changes.	
Expert advisors			
	• estimate the average number of oxygen bottles a year that might be required for a patient at home as abortive therapy for chronic cluster headaches	1:Patients with chronic cluster headache use oxygen with every cluster attack and some get 6-8 attacks per day so a whole cylinder might be consumed in less than a week. 2:depends on whether the sufferer is episodic or chronic. An average sufferer has 2 attacks per day during a cluster headache cycle. For each headache oxygen is recommended at 12-15 litres per minute for upto 15 minutes therefore during each cluster episode about 180 litres could be used. The size of the	

		cylinder varies but I think holds 1360 litres therefore may last 7-10 days?	
	• estimate a typical cost per bottle	1:Sorry I cannot answer this question as I am not a party to when it comes to buying and selling of the product 2:no idea	
	• or alternatively, a cost of providing oxygen per year per patient at home	1:I cannot answer the question. 2:no idea	
	• would you expect patients using gammaCore to also be treating attacks using medication such as Sumatriptan, Zolmitriptan and Oxygen?	1:If Gammacore produces a good response, I would not expect patients to use either of the above options 2:yes	
	• where someone might be classed as a "non-responder" to standard care (Sumatriptan, Zolmitriptan and Oxygen) would you expect that they might still be using these medications for either preventative or acute treatment of cluster headache attacks? In the model "non-responders" are those whose frequency of attacks is reduced by less than 50%.	1:If the preventive treatment only reduces the attacks severity or frequency to less than 50% and are classed as non-responders, I expect them to be still using acute treatments with oxygen or triptans 2:yes	
	Patient population and pathway 1. Please estimate the number of patients with cluster headaches that you treat each year	150	
	2. What proportion of these patients have chronic vs episodic cluster headaches (roughly)?	Episodic 30 Chronic 120	
	3. Are there patients with cluster headache who are not being treated (i.e. are the numbers treated reflective of the UK prevalence)	No	
	4. Can you describe a typical pathway to diagnosis? For example, does the GP diagnose cluster headache and refer to the specialist and how long might the process for referral take?	We make the diagnosis and perform investigation and start treatment	

<table>
<tr>
<td></td>
<td>5. When would a patient be described as “treatment refractory”?</td>
<td>Once they have failed the three most commonly used treatments i.e. verapamil, topiramate and lithium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>
Resource use
6. Please could you review the table below and comment on how well it fits with your experience of treating patients with chronic cluster headaches
a. For patients with chronic cluster headaches refractory to medication, receiving standard care
<table>
<tr><th></th><th>Doses per 14 days</th><th>Dose</th><th>Comments</th></tr>
<tr><td>zolmitriptan</td><td>1.30</td><td>5mg/0.1ml nasal spray</td><td></td></tr>
<tr><td rowspan="3">sumatriptan</td><td rowspan="3">7.50</td><td>Split between :</td><td rowspan="3"></td></tr>
<tr><td>87% : 6mg/0.5ml subcutaneous inj</td></tr>
<tr><td>13%: sumatriptan 10mg/0.1ml nasal spray</td></tr>
<tr><td>oxygen doses</td><td>10.80</td><td>20 minutes use</td><td></td></tr>
</table>
</td>
<td>This varies from patient to patient as patients with chronic cluster headaches use up to two injections of sumatriptan a day and even more and this is in addition to the oxygen treatment that they use every day depending upon the number of attacks</td>
<td></td>
</tr>
</table>

<table>
<tr><td></td><td>b. For patients with chronic cluster headaches refractory to medication, receiving prophylactic gammaCore treatment and experiencing at least a 50% reduction in frequency of attacks
<table>
<tr><th></th><th>Doses per 14 days</th><th>Dose</th><th>Comme</th></tr>
<tr><td>zolmitriptan</td><td>0.6</td><td>5mg/0.1ml nasal spray</td><td></td></tr>
<tr><td rowspan="3">sumatriptan</td><td rowspan="3">2.5</td><td>Split between :</td><td rowspan="3"></td></tr>
<tr><td>87% : 6mg/0.5ml subcutaneous inj</td></tr>
<tr><td>13%: sumatriptan 10mg/0.1ml nasal spray</td></tr>
<tr><td>oxygen doses</td><td>2.2</td><td>20 minutes use</td><td></td></tr>
</table></td><td>This would reduce the consumption by at least 50% if there is a 50% reduction in the frequency of the attack.</td><td></td></tr>
<tr><td></td><td>7. Does the proportion of sumatriptan doses (for abortive treatment of attacks) that are subcutaneous (87%) or via nasal spray (13%) reflect with your own experience?</td><td>Yes</td><td></td></tr>
<tr><td></td><td>8. How often would a review or other appointment be required specifically for gammaCore? Who would be likely to carry out the review, and in what setting?</td><td>If they are on a gammacore and nicely controlled than I need to see only once a six months</td><td></td></tr>
<tr><td></td><td>9. If gammaCore review is added into a routine review, how much additional time does it require, and does it require any change in the staff who do the review?</td><td>No additional time.</td><td></td></tr>
<tr><td>Asked to 1 expert only</td><td>Is occipital nerve block used for chronic cluster headache in the UK currently?
If so, can you give any indication of how widespread its use is?</td><td>As far as I am aware it is practiced widely in every headache centre in the UK and is used for both episodic and chronic cluster headache as a rescue treatment for a short term benefit similar to oral steroids.</td><td></td></tr>
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Appendix 1

Appendix 2 [Insert additional appendices as required]

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

MT323 Gammacore for Cluster Headaches

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from [insert EAC] to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **[insert date]** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

[Insert date submitted to Sponsor]

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Executive Summary "The EAC noted that the model is highly dependent on an initial free trial period and reducing the use of abortive medication."	We propose that the statement regarding the initial free trial be removed.	The periods following the initial free of charge 93-day evaluation are cost saving in the base case and either cost saving or cost neutral in the majority of scenarios modeled, and to state that the model is "highly dependent on the free trial" is misleading. electroCore has made a clear commitment to providing a free evaluation period, and recognises that there is uncertainty regarding which patients will respond to gammaCore.	No change has been made. The EAC understand that there is a commitment to a free evaluation period, but feel it is important to understand how key this is to the economic modelling results. It has not always been present historically, and pricing structures can change. Without the free trial period the base case is cost incurring. Although periods following the 93-day evaluation are cost saving, this is because patients for whom gammaCore is less effective have already stopped using it.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Executive Summary "The EAC noted that the model is highly dependent on an initial free trial period and reducing the use of abortive medication."	We propose adding a statement after this "Modelling cost savings from reduction in abortive medication only is likely to be a conservative estimate, as there may be further resource use savings from reductions in GP and outpatient appointments, adverse events associated with abortive medication, use of	In the "Additional assumptions identified by EAC" appended to table 8, the EAC recognizes that there may be further cost savings from reduced GP/outpatient appointments and AEs. Furthermore, in the UK Marin study	No change has been made. The statement is correct, and the possible further savings have already been noted in the main report.

	prophylactic medication and rental costs of oxygen tanks."	some patients discontinued prophylactic medicine and oxygen altogether. These potential cost savings, although discussed in the submission, were not reflected in the model.	

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 2.1 "The EAC noted a minor error in the last paragraph of section 3.1 where the pain free period for episodic cluster headaches was described as being one month when in fact the pain free period for episodic cluster headaches is at least 3 months according to the International Classification for Headache Disorders (ICHD)."	No amendment required, just to note that the ICHD classification has only recently changed, and at time of submission the definition we provided was correct.		Thank you for the clarification.

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Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 1, 'Cost analysis' "The submitted economic model considered chronic cluster headache only. The rationale given for this was that UK based evidence suggests that chronic cluster headache is more prevalent."	Removal of the second sentence "The rationale given for this was that UK based evidence suggests that chronic cluster headache is more prevalent."	We do not state that chronic cluster headache (cCH) is more prevalent than episodic cluster headache (eCH). We acknowledge that eCH is more prevalent that cCH. In the submission we state "Given the lack of data to build an economic case in episodic use, and the small numbers of eCH patients likely to be offered gammaCore in the UK (1 out of 30 patients in the UK Marin study), eCH has not been considered in the cost analysis." This is not stating that cCH is more prevalent, rather that eCH patients have in the past been less likely to be offered gammaCore by clinicians.	Thank you for your comment, this has been amended to more accurately reflect the submission text. "The submitted economic model considered chronic cluster headache only. The rationale given ~~for this~~ was that UK based evidence suggests ~~that~~ only small numbers of patients with ~~chronic~~ eCH ~~cluster headache is~~ are ~~more~~ likely to be offered gammaCore in the UK~~prevalent~~."

NICE National Institute for Health and Care Excellence

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.2, Table 2 and Section 3.5 The EAC states that patients in the PREVA study (Gaul et al. 2016) are not truly treatment refractory.	We would request that the EAC amend these statements throughout.	The average time since the onset of cCH in the PREVA study was approximately 5 years. By definition, that reflects a patient population reporting between 3-8 attacks per day for the significant majority of the year. Despite the best available acute and preventative standard of care, the patients in PREVA were suffering from more than 16 acute attacks per week. This clearly demonstrates that although they might be able to use existing medication on occasion, these medications were no longer fully effective, tolerated or available. We believe this matches a practical definition of refractory that is based not only on a specific contraindication to existing therapies, but the inability of the existing medications to adequately treat the disease, the patients inability to tolerate the existing medications, or the inability to use sufficient quantities of existing medications.	Thank you for your comment. The EAC note that this information is not detailed in the PREVA study and no definition for treatment refractory patients is included in the publication nor do the inclusion criteria provide any evidence that the population was treatment refractory. The EAC accept that while this information may be accurate, only the information in the published paper can be assessed and appraised and any conclusions made must be drawn from published, verifiable sources. The EAC suggest that no change should be made to the assessment report at this time but acknowledge that this may be a point for discussion among the clinical experts.

NICE National Institute for Health and Care Excellence

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 3.5 "Although randomised trials are generally considered to provide the best quality evidence, GRADE assessment (Appendix C) suggests that the certainty of the evidence for the outcomes of interest ranges from moderate to very low."	A review of the GRADE assessments	Table 5 of the following publication states different GRADE assessments to those proposed by the EAC; https://jnnp.bmj.com/content/jnnp/early/2019/04/05/jnnp-2018-320113.full.pdf	The EAC acknowledge that the assessments proposed differ to those in the paper highlighted (Reuter et al, 2019) however, the outcomes for which GRADE has been applied to have not been listed in Table 5 (Reuter et al. 2019) therefore a comparison of 'Certainty' cannot be made. The EAC suggest that the reason for the difference is that the GRADE assessment carried out by the EAC was conducted to assess the quality of the whole body of evidence related to each outcome rather than applying the GRADE assessment to individual studies as seems to be that case in the Reuter study. An overall GRADE quality rating is applied to a body of evidence across **outcomes** not individual studies (https://bestpractice.bmj.com/info/toolkit/learn-ebm/what-is-grade/) See also NICE manual for example of GRADE profile table

			https://www.nice.org.uk/process/pmg20/resources/appendix-h-pdf-2549710190

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 4.5 "The submission correctly states that all models found gammaCore to be cost-effective, and that the UK adaptation of the German model found an ICER of £166.12/QALY gained. However it is not correct to state that this demonstrates cost savings for gammaCore compared with standard care. Cost savings were found in German and USA settings, but the UK adaptation found gammaCore to be cost incurring."	Reconsider the wording so that it does not imply that we state that the results of this publication suggest cost savings in the UK, because we do not.	The submission states "One published study (Morris et al. 2016) that compared use of gammaCore plus SoC vs. SoC reported cost savings after one year of 414 euros." This clearly relates to the German results and not the UK results, which were based on a probabilistic analysis and therefore not directly comparable to the model results, which were deterministic. Furthermore, the price of gammaCore resulting in the UK ICER was not disclosed in the publication. In addition it is highly important to note that the pricing structure of gammaCore at the time of this study and analysis was different to that in place now. At the time of analysis the gammaCore devices being utilised in the UK were only able to deliver a total of 300 doses	Thank you for your comment, we have re-worded the statement: The submission correctly states that all models found gammaCore to be cost-effective, and that the UK adaptation of the German model found an ICER of £166.12/QALY gained. Although cost savings were found in German and USA settings, the UK adaptation found gammaCore to be cost incurring."

		before the device needed replacing. These first-generation gammaCore devices typically expired every 50 days with a patient being instructed to use 6 doses per day. The historical cost of each 300-dose device was £438, which equated to a daily cost of £8.76; furthermore patients were restricted to stimulating 6 times per day. The current 93-day dosing cycles cost £625, a daily cost of £6.72; with patients able to stimulate up to 30 times a day.	

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8. "Patients are reassessed every 3 months for ongoing response and non-responders in the gammaCore plus SoC group discontinue prophylactic treatment with gammaCore." "The model does have options to work in this way, but the base case has no change in the	Consider removing the last sentence	This was explored via the sensitivity analyses examining different rates of loss of response.	Thank you for your comment. The EAC statement is correct, however we have added a sentence to reflect the sensitivity analysis: "The model does have options to work in this way, but the base case has no change in the proportion of responders and non-responders after the initial month. It is included in sensitivity analysis."

proportion of responders and non-responders after the initial month."			

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 8. "Discontinuation occurs in 3-month blocks in line with prescriptions for a gammaCore refill." "This is the model submitted by the manufacturer, other time periods have been used historically. In the base case there is no discontinuation except after the initial trial."	Consider amending to "Each prescription enables a time-limited refill of gammaCore therapy for up to 93 days". As a response assessment is required for further refill, discontinuation occurs in 3-month blocks. The model submitted by the manufacturer is in line with the current time-limited refill period in the UK. While the base case assumes no discontinuation except after the initial trial, scenarios were included that examined the impact of loss of response and subsequent discontinuation."	As explained in Issue 6 - Historically nVNS therapy delivered via gammaCore was made available in a different format to that currently in operation. Whilst therapy was previously dose limited, it is now time limited to 3-month blocks. The sensitivity analyses, does examine different rates of loss of response after the initial trial.	Thank you for your comment. The EAC statement is correct, however we have added a sentence to reflect the sensitivity analysis: "This is the model submitted by the manufacturer, other time periods have been used historically. In the base case there is no discontinuation except after the initial trial. It is considered in sensitivity analysis."

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Section 4.9 "We have identified small errors in the calculations for utilities, but these do not affect the base case."	Please remove this sentence.	The economic evaluation was a cost analysis only and we do not understand why an error in utilities is mentioned.	We have removed this sentence, as the utilities are not used in the submission.

		Furthermore, as no detail of the error was provided, we have no opportunity to respond to the statement.	