NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: Alpha Stim AID for Anxiety (MT477)

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. **Addendum report 1 (Ongoing study with the AIC)** – an addendum to the EAC assessment report.
3. **Addendum report 2 (Economic Model) -** an addendum to the EAC assessment report.
4. **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.
5. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
6. **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.
7. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
8. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
9. **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.

10. **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.

Document cover sheet

Assessment report: MT477 Alpha-Stim AID

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Version number	Brief description of changes	Author/reviewer (e.g. J Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
0.1	Notes to help with write up First draft written	HM JW	20/05/2020 29/05/2020	
0.2	Draft writing – clinical section	JW and HM	09/06/2020	
0.3	Draft writing – clinical section	JW	17/06/2020	
0.4	Draft writing – clinical section and economic search sections Addition of quality assessments	HM and JW	25/06/2020 29/06/2020	
0.5	Review of clinical section (v0.5) Draft writing economics section versions 0.1 to 0.3	HM and JW SOC and AC	02/07/2020 09/07/2020	
0.6	Merge clinical section (v0.5) with economics section (v0.3) for draft report to NICE	JW	10/07/2020	10/07/2020
0.7	Address comments from NICE in clinical section. Final QA of clinical evidence. Review of draft report	JW HM GCR	14/07/20	
0.8	Complete economics section	SOC	21/07/20	
0.9	Merged clinical and economics sections. Formatting checks.	JW	21/07/20	
0.10	Executive summary and conclusions. Review and sign-off.	SOC and JW GCR	21/07/20	
0.11	Final review	JW, SOC, AC	22/07/20	
1.0	Final report		23/07/20	23/07/20

1.1	Address comments in company fact check	JW	28/07/20	
1.2	Address comments in company fact check	SOC	28/07/20	
1.3	Review changes	GCR	29/07/20	
2.0	Final report (following company fact check)		29/07/20	29/07/20
3.0	Ammendments following expert input	SOC (checked by AC and JW)	28/08/20	28/08/20
3.1	Ammendment following NICE coments	JW, AC	28/08/20	28/08/20
3.2	Review changes	SOC		
3.3	Minor amendments	JW	05/10/20	05/10/20

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance
MT477 Alpha-Stim AID for anxiety disorders
External Assessment Centre report

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Number of attached appendices: 13

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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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
AIS	Athens Insomnia Scale
BAI	Beck Anxiety Inventory
BDI	Beck depression inventory
BNF	British National Formulary
BPI	Brief Pain Inventory
BSI	Brief symptom inventory
CAM	Complementary and alternative medicine
CASP	Critical Appraisal Skill Programme
CBT	Cognitive behavioural therapy
CD	Cannot determine
CES	Cranial electrotherapy stimulation
CCG	Clinical Commissioning Group
CGI-I	Clinical Global impression- Improvement Scale
CGI-S	Clinical Global Impression – Severity Scale
CGI-SI	Clinical global impression severity of illness
CI	Confidence interval
COI	Conflict of interest
DHSC	Department of Health and Social Care
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 9th Edition
EAC	External Assessment Centre
EDR	Electrodermal response
EEG	Electroencephalogram
EMG	Electromylegram
ESAS	Edmonton Symptom Assessment Scale
FDA MDR	US Food and Drug Administration Medical Device Reporting
FDADS	Four Dimensional Anxiety and Depression Scale
GAD	Generalised anxiety disorder
gCBT	Group cognitive behavioural therapy
GP	General Practitioner
GSI	Global severity index
HADS	Hospital anxiety and depression scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D17	Hamilton Depression Rating Scale
IAPT	Improving Access to Psychological Therapies
iCBT	Individual cognitive behavioural therapy
ICD-11	International Classification of Diseases 11th Revision
ICTRP	International Clinical Trials Registry Platform
IQR	Interquartile range
ITT	Intention to treat
LOCF	Last observation carried forward
LTC	Long term condition
MAD	Mixed anxiety and depression disorder
MAUDE	Manufacturer and User Facility Device Experience
MCAR	Missing completely at random
MDAS	Modified Dental Anxiety Scale
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
MUS	Medically unexplained symptoms
NA	Not applicable
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
NR	Not reported
OCD	Obsessive compulsive disorder
PCS	Pain Catastrophizing Scale

PGI-I	Patient global impressions – improvement
PHQ-9	Patient Health Questionnaire -9
POMS	Profile of mood state
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Problematic Sensitive Analysis
PSDI	Positive symptom distress index
PST	Positive symptom total
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-traumatic stress disorder
PWP	Psychological Wellbeing Practitioner
QOL	Quality of life
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
SAS	Self-rating anxiety scale
SD	Standard deviation
SDS	Self-Rating Depression Scale
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
STAI	State trait anxiety inventory
SUD	Subjective Units of Distress Scale
UCLA	University of California Los Angeles
VAS	Visual analogue scale
WASA	Work and Social Adjustment Scale
WHO	World Health Organisation
WHOQOL	World Health Organisation, Quality of Life

Figures and Tables in EAC report

Executive summary

The company included 24 studies in total in their clinical evidence submission on Alpha-Stim AID Cranial Electrotherapy Stimulation (CES) Device as a treatment for anxiety disorders. The EAC included 5 published studies and 1 unpublished study which were relevant to the decision problem following a systematic literature search. These 6 studies were 3 RCTs and 3 non-comparative observational studies, all of which have undergone critical appraisal. The included studies are small and all are at risk of bias. Overall the published evidence suggests that patients with generalised anxiety disorder may benefit from using Alpha-Stim AID.

Included studies report statistically significant improvements in anxiety symptom scores (measured using validated questionnaires in all but one study) in participants with anxiety disorders treated with Alpha-Stim. The long-term benefit is unclear as only one study followed up patients for more than 6 weeks; this non-comparative study showed anxiety symptom improvements were sustained at 24 weeks. Only one of the five published studies (prospective, non-comparative, observational) is set in the UK NHS which is highly relevant to the decision problem. The generalisability of the other studies is more limited. Differences between the studies in their design, setting, interventions, and outcome measures makes meta-analyses inappropriate, therefore the extent and certainty of the benefit is difficult to determine.

The EAC conclude that Alpha-Stim is a suitable non-pharmaceutical treatment option for patients with generalised anxiety disorder who have not responded to low intensity psychological interventions (individual non-facilitated self-help, individual guided self-help and psychoeducational groups) in step 2 of the stepped pathway for the management of generalised anxiety disorder. Current standard of care for such people is a choice of an individual high-intensity psychological intervention (such as individual CBT (iCBT) or individual applied relaxation) or a drug treatment. The company's claimed benefit that Alpha-Stim reduces anxiety symptoms is supported by the evidence, albeit of a low quality.

There is no evidence comparing Alpha-Stim directly to individual high-intensity psychological interventions. One RCT showed improved anxiety symptoms in patients treated with Alpha-Stim and the drug paroxetine compared to paroxetine alone. The company's claimed benefit that Alpha-Stim reduces reliance on medications is not supported by the evidence, and neither is the claim that Alpha-Stim is an improved treatment in subgroups where additional medication is contraindicated. The available evidence does not support its use as a replacement for high-intensity interventions such as iCBT. The EAC and experts note the importance of an alternative option for treating patient with generalised anxiety, and that the decision to use Alpha-Stim should be made between the treating clinician and the patient.

Adverse events from Alpha-Stim use are rare and self-limiting and the EAC concludes that use of Alpha-Stim does not raise any safety concerns.

The economic analysis suggests that Alpha-Stim is likely to be cost-saving compared to iCBT as presented by the company. The EAC consider that the proportion of patients who agree to use Alpha-Stim is not likely to be 100% of patients offered the device and consider these patients while not incurring the cost of Alpha-Stim, will incur the cost of iCBT directly. In addition, the EAC consider medication use should be included in the analysis and iCBT should be included as a single cycle but with the number of sessions within the cycle varying. In the EAC base case only 22% of patients take up the offer of Alpha-Stim and a proportion of patients will choose medication as a treatment option. In the EAC base case, Alpha-Stim remains cost saving, however the savings are greatly reduced compared with those presented by the company. A key driver in both the adjusted EAC model and the alternative EAC base case is the rate of uptake of Alpha-Stim, with greater cost savings achieved with higher uptake. The company's claimed benefits that Alpha-Stim represents a reduced cost for treatment of anxiety compared to iCBT, and that there is a reduced need for iCBT, are supported by the evidence, although the EAC recognise that the extent of the cost saving may be lower than that presented by the company.

The key weaknesses in the current economic analysis are related to the rate of uptake of Alpha-Stim and medication use. The EAC notes that the true clinical scenario is likely to be a complex mix of treatments with some patients taking medication as well as iCBT or Alpha-Stim treatment, some patients having a preference for medication and some patients having a preference for non-pharmacological treatments.

In addition, the EAC notes that careful consideration should be given to the response rates to treatment as it is possible that patients who do not respond to their first non-pharmacological treatment may not achieve a good response to the second treatment as is currently modelled.

The company's claimed benefit that patients can re-use Alpha-Stim devices in their homes is partially supported by the evidence. Studies show that patients are able to use the device in their home, however the pathway proposed by the company is that patients have one or two 6 week cycles of Alpha-Stim and then return the device to their NHS provider.

Despite weaknesses in the evidence base, it is the EAC's opinion that the available evidence on Alpha-Stim as a treatment for generalised anxiety disorder does support the case for adoption in the NHS.

1 Decision problem

The company has proposed a variation to the population in the decision problem. The rationale provided is that there is evidence available to support the use of the device in patients who have symptoms of anxiety as well as those with a diagnosis of anxiety. Whilst the EAC accept that the technology could be beneficial to a broader population who report symptoms of anxiety or may be at risk of experiencing anxiety, this assessment is focused on Alpha-Stim as a treatment for people with a diagnosis of anxiety. As such the EAC have not accepted this change to the scope.

No further changes were proposed to the decision problem.

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	People with anxiety disorders.	People with anxiety symptoms but have not yet been diagnosed for anxiety disorders.	This assessment is focused on Alpha-Stim as a treatment for people with a diagnosis of an anxiety disorder.
Intervention	Alpha-Stim AID	Unchanged	Not applicable
Comparator(s)	Pharmacological interventions (e.g. selective serotonin reuptake inhibitors) Psychological interventions (e.g. group or individual CBT)	Unchanged	Not applicable
Outcomes	• The outcome measures to consider include: • Anxiety and depression symptoms scores • Social and occupational functioning • Quality of life	Unchanged	Not applicable

	• Use of psychological interventions Use of pharmacological interventions Number of GP visits • Waiting time for psychological treatments • Pharmacological related adverse events such as overdose		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect 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 of combinations of devices are needed.	Unchanged	Not applicable
Subgroups	• People who also have other mental health disorders such as depression • People with other comorbidities (i.e. chronic conditions) • Severity of anxiety	Unchanged	Not applicable
Special considerations, including issues related to equality	The condition can have a significant effect on individuals' daily lives. This may mean someone disabled in their anxiety disorder has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act.	Unchanged	Not applicable

The EAC has used the International Classification of Diseases 11th Revision (ICD-11) to define the term anxiety disorder. The following conditions are categorised as anxiety or fear related disorders:

- Generalised anxiety disorder
- Panic disorder
- Agoraphobia
- Specific phobia
- Social anxiety disorder
- Separation anxiety disorder
- Selective mutism
- Substance-induced anxiety disorders
- Hypochondriasis

- Secondary anxiety syndrome
- Other specified anxiety or fear-related disorders
- Anxiety or fear-related disorders, unspecified

The following conditions are not categorised as anxiety or fear related disorders in ICD-11 and therefore have not been included in this evidence review:

- Post-traumatic stress disorder
- Obsessive compulsive disorder
- Mixed anxiety-depressive disorder
- Tic disorders

2 Overview of the technology

The Alpha-Stim AID Cranial Electrotherapy Stimulation (CES) Device is a Class IIa CE marked medical device manufactured by Electromedical Products International Inc (Mineral Wells, Texas, USA). Documentation relating to the CE mark (instructions for use, declaration of conformity, and appropriate medical device directive certificate) have been provided to the EAC and checked. The indicated use is cranial electrotherapy stimulation for the treatment of anxiety, insomnia, depression and pain. The device is portable and can be self-administered at home, or by a healthcare professional in a hospital or clinic setting. Alpha-Stim AID uses CES, providing variable electrical microcurrent to the brain which stimulates alpha wave electrical activity. The current is applied by clips that attach to the ear lobes. The device has a pulse repetition rate of 0.5 hertz. The wave is composed of bipolar asymmetric rectangular waves in a cycle that repeats periodically at 10-second intervals (NICE, 2019). The device is non-invasive, non-pharmacological, and can be used as an adjunct to pharmacological or psychological treatment or on its own (Morriss et al. 2019).

The device is the size of a mobile phone and has a pair of small clips which are wetted with a conducting solution. When it is turned on, a small vibration is felt in the ears, like a mild electrical current. The strength of this can be adjusted. Alpha-Stim AID can be used for between 20 and 60 minutes every day, every other day, or on an as-needed basis. The higher the strength of the

current, the shorter the time the patient needs to wear it. Alpha-Stim AID is battery powered, which allows users to be mobile when using it (NICE, 2019).

The device uses 2 AAA 1.5 volt lithium batteries which are replaceable. Currently the device is not rechargeable, although the company states that this is a likely future development.

The Alpha-Stim AID kit comprises the following components:

- Alpha-Stim AID device
- Earclip electrodes
- Conducting solution (50 ml) plus empty bottle
- Electrode pads (felt like pads which stick to the Earclip electrodes)
- User manual1
- USB multilingual owner's manual
- Lanyard
- Storage case
- 2 AAA 1.5 volt lithium batteries

The company has presented a list of 7 previous versions of the Alpha-Stim device which were available from 1981 until 2012, plus the present Alpha-Stim AID available from October 2012 until present day. The company state that all versions of the device are based on the same mechanism of action, and that differences between versions relate to features and presentation of the device only. The EAC accepts the manufacturer's claim that evidence from older generations of the Alpha-Stim device is generalisable to the current device.

3 Clinical context

The company have presented 3 clinical pathways where Alpha-Stim AID may potentially be used to treat GAD:

1. Primary care GP Services;
2. Primary care Improving Access to Psychological Treatment (IAPT);

3. Secondary care mental health or long-term conditions pathway.

The EAC has identified the NICE GAD clinical pathway (NICE CG113) to be relevant to the pathways presented by the company. The EAC has also provided a description of the IAPT service which is commonly used in England to deliver relevant NICE-recommended therapies.

NICE Generalised Anxiety Disorder (GAD) pathway

The two primary care pathways presented by the company relate to a patient presenting to a GP setting or self-referring to an IAPT service, and then being diagnosed with GAD. The NICE Clinical Guideline on Generalised anxiety disorder and panic disorder in adults: management (CG113) pathway is referenced which is appropriate. The EAC has presented a more complete description of the stepped care model (Figure 1 and Appendix A).

In their two primary care pathways, the company proposes that Alpha-Stim is used as an alternative treatment option to drug treatment and high intensity psychological interventions after steps 1 and 2 of the GAD pathway. These would be patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective. This means that Alpha-Stim could be offered to patients as a treatment instead of individual CBT (iCBT) or drugs. Patients often have to join a waiting list for iCBT; Alpha-Stim may also be a treatment option for patients whilst they wait for iCBT. For patients who choose to use Alpha-Stim, and respond to one or two courses of treatment (remission is a GAD-7 questionnaire score of 7 or below), they would be discharged and not go on to have iCBT. For patients who choose to use Alpha-Stim and do not respond to it (GAD-7 questionnaire score of 8 or above), they would go on to receive iCBT or drug treatment (as in the current GAD pathway). For patients who choose not to use Alpha-Stim, iCBT and drugs remain as their standard treatment options.

Two clinical experts stated that Alpha-Stim could be a useful treatment option earlier in the pathway after step 1, in which case the comparator treatments would be low-intensity psychological interventions.

The company has submitted minor amendments to the proposed pathway. The company's final proposed pathways for primary care and IAPT state that Alpha-Stim would be offered to patients with GAD diagnosed using a GAD-7 questionnaire score of at least 8 (amended from a score of at least 10). This is in line with the IAPT pathway definition of a clinical case. Three experts noted that diagnosis of GAD in primary care can also use clinical features as well as a questionnaire.

The patient would be provided with an Alpha-Stim AID and shown how to use it by either a practice nurse or health care assistant (primary care GP pathway) or an IAPT Psychological Wellbeing Practitioner. The original submission suggested also that the company could provide the Alpha-Stim AID directly to patients but the company has since confirmed to the EAC that this is not the case.

The patient then takes the Alpha-Stim device away to use at home for 6 weeks. The company propose daily use of the device for 60 minutes for 6 weeks, with telephone support within 72 hours. The company communicated to the EAC that telephone support should be provided by the practice nurse.

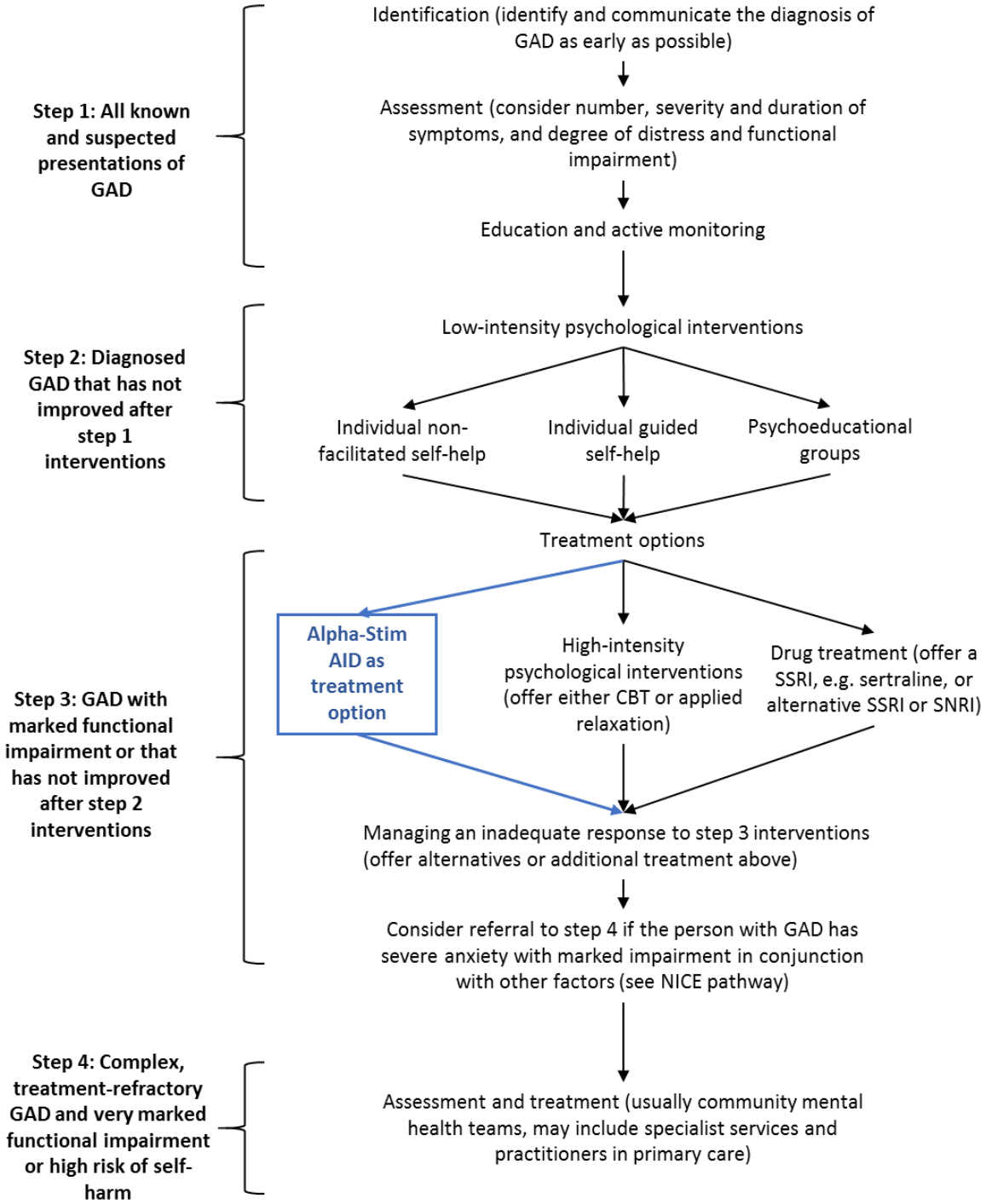
The company provided the following information to the EAC during the fact check process: "Proposed model for treatment is 60 minutes daily, which is consistent with research use of AID, where it is important that all variables be controlled. Actual clinical duration of each treatment is dependent upon tolerable current levels for each patient. Dosage is defined as current inversely proportional to time (i.e., the higher the current the quicker the treatment). Consistent with the Instructions for Use for Alpha-Stim AID, the patient should increase current slowly (500 μA is the highest setting) until a slight vertigo is experienced (a dizzy feeling, similar to the sensation of rocking on a boat), then decrease immediately until the dizziness stops. 20 minutes is enough time for most people if the current is set to at least 250 μA. 40 minutes to 1 hour is recommended if the current is at or below 200 μA."

Following the initial 6 weeks of treatment with Alpha-Stim, the following options are available:

- Stop the Alpha-Stim treatment when the GAD-7 score reaches 7 or below (this is remission as measured by IAPT services).
- If appropriate, give 6 weeks more Alpha-Stim treatment if patient has a GAD-7 score ≥8. At this point patients may also be referred for other high-intensity treatments.

The NICE GAD pathway Step 4 is the most relevant pathway to the secondary care mental health setting (the third pathway presented by the company). Details of the pathway for management of GAD based on NICE CG113 are presented in Appendix A.

Figure 1 - NICE pathway for Generalised anxiety disorder (GAD): Stepped-care model (based on CG113) with Alpha-Stim AID inserted as treatment option (produced by EAC)



Improving Access to Psychological Treatment (IAPT)

Improving Access to Psychological Therapies (IAPT) services provide evidence-based psychological therapies to people with anxiety disorders and depression. According to one expert, IAPT teams are the standard structure of service provision for people with anxiety and depression in England. IAPT is not available outside of England. IAPT teams deliver the NICE-recommended stepped-care model for GAD including step 2 (low-intensity interventions) and step 3 (high-intensity interventions) with or without concurrent pharmacological treatment which is typically managed by the GP (National Collaborating Centre for Mental Health, 2018). Referral pathways to IAPT include self-referral, community or voluntary service referral, primary care referral, and secondary care referral (including both mental health and physical health care services) (Figure 2).

IAPT services for people with long-term conditions and medically unexplained symptoms (IAPT-LTC services)

IAPT-LTC services provide evidence based (NICE-recommended) psychological therapies for people with LTCs who also have depression and anxiety disorders, or who have medically unexplained symptoms (MUS). While some services will be hospital based, it is expected that most will be embedded in primary care and community settings. IAPT-LTC services are built on the same key principles that underpin the IAPT programme.

A wide range of NICE guidance is available for the treatment of depression and anxiety disorders in the general population, for LTCs and for specific diagnostic groups of MUS. Where depression and anxiety disorders are comorbid with LTCs there is more limited guidance (NHS England & NHS Improvement, 2018).

NHS England's expert advisory group recommended that the psychological therapies that are already used in IAPT services should be deployed in IAPT-LTC services. As such, use of the Alpha-Stim device would follow the same pathway as that described above for the NICE GAD pathway.

Special considerations, including issues related to equality

NICE's scope states that anxiety disorders can have a significant effect on individuals' daily lives. This may mean someone is disabled if their anxiety disorder has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act. People from certain socially excluded groups who would benefit from psychological interventions might be less likely to access them, such as black, asian and ethnic minority groups; older people; those in prison or in contact with the criminal justice system; and ex-service personnel. Young women are more likely to have anxiety disorder. Sex and age are all protected characteristics under the Equality Act 2010.

The company did not identify any additional concerns or considerations. The EAC did not identify any further equality issues.

4 Clinical evidence selection

This information in this assessment report relates to the Alpha-Stim AID CES Device.

4.1 *Evidence search strategy and study selection*

The company's search strategy was simplistic and used only free text terms (no Medical Subject Headings) and searched a limited selection of resources (Google Scholar, PubMed, PubMed Central). To ensure that all relevant research had been identified, the EAC conducted their own systematic search, to include periods from 1st January 1980 to the 12th May 2020 (Appendix B). Nine bibliographic databases and two clinical trial registries were searched using a range of free text terms and subject headings; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the MAUDE database were searched for adverse events.

The literature searches identified 285 references; these were screened by title and abstract in accordance with the decision problem by one researcher, 31 were selected for further screening and full texts were retrieved and reviewed by one researcher. Queries were checked by another researcher to make a

final eligibility decision, and all studies included by the company were also checked by another researcher to make a final decision on inclusion. The EAC identified six studies which met NICE's scope, all of which had also been identified by the company. Details of the EAC search are provided in appendix B.

4.2 *Included and excluded studies*

The following table summarises the number of studies included by the company and the EAC at each stage in the process. A summary table of EAC decisions for individual studies is provided in Appendix C.

		Company submission	EAC search	
			Within scope	Relevant but outside of decision problem*
Number of studies identified in a systematic search		35	285	
Number of studies identified as being relevant to the decision problem.		24	6	7
Of the relevant studies identified:	Number of published studies	21	5	7
	Number of abstracts	1	0	0
	Number of ongoing or unpublished studies	2	1	0
*These are studies which were outside of the decision problem because the population did not have a diagnosed anxiety disorder but were considered relevant to the assessment because they included people experiencing anxiety symptoms.				

The EAC included 5 published studies (Bystritsky et al. 2008; Barclay & Barclay 2014; Morriss et al. 2019; Lu & Hu 2014; Overcash 1999) and 1 unpublished study (Voris 1995) as key evidence which are presented in table 1. All except Bystritsky et al. (2008) were also included by the company. The company excluded this study because the sample size was too small but the EAC has determined that it meets the scope of this appraisal and that a small sample size is not a valid reason to exclude the study. All 6 included studies

have undergone full critical appraisal (Appendix D), and presentation of methodology and findings by the EAC (section 5).

Studies excluded by the EAC are summarised in Appendix E with reasons given for exclusion. The main reason for the disparity in the number of included studies between the company and EAC is that the company included studies of people with anxiety symptoms or where anxiety-related outcomes are reported. In contrast, the EAC considered that only studies with a population with a diagnosis of an anxiety disorder meet the decision problem in the scope and should be included.

The EAC does not consider findings from studies of people without a confirmed anxiety disorder diagnosis to be generalisable to the decision problem. However, in order to present all evidence which may be of relevance to the decision problem, the EAC has presented studies which include people experiencing anxiety symptoms (Table 2). The criteria used by the EAC to select studies for presentation as potentially relevant were: i) the study population included participants with anxiety symptoms; ii) the setting or pathway was relevant to the current decision problem, for example, studies which were carried out in a non-clinical setting, were excluded. The EAC reviewed all 26 studies in the company submission (24 included and 8 excluded studies, minus the 6 studies included as key evidence) against the criteria for deciding if the findings may be relevant to the decision problem. Seven studies were selected as being out of scope but with potentially relevant outcomes (they did not undergo full critical appraisal) (Chen et al. 2007; Gibson & O'Hair 1987; Kirsch et al 2014; Koleoso et al. 2013; Libretto et al. 2015; Winnick et al 1999; Yennurajalingam et a. 2018) (Table 2). Studies which did not meet these criteria were completely excluded (Appendix E).

Table 1 – Methodology of 6 studies included by the EAC in the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Comparative studies				
Barclay & Barclay (2014) USA n=115	**Design:** Double blind, sham controlled, randomised controlled trial. **Intervention:** Alpha-Stim 100 (n=60). Patients treat themselves daily for 1 hour for 5 weeks. Current intensity was pre-set and locked at 100 μA (subsensory level). Participants were provided treatment logs to document the day, time, and duration of treatment. **Control:** Sham device (n=55) for 5 weeks. The sham CES devices were identical to the active device, except the ear clip electrodes did not emit electricity **Funding:** Unfunded study that took place in private practice setting. No COI reported. **Status:** Published 🟢	**Participants:** Adults with primary diagnosis of anxiety Comorbid depression allowed. **Setting:** USA (central Virginia), private primary care setting 🟡	**Co-primary outcomes:** HAM-A (anxiety) and HAM-D17 questionnaires at weeks 1, 3, and 5. Response to treatment was defined as a ≥50% reduction in HAM-A and HAM-D17 measures. **Secondary:** None. **Follow-up:** Measurements took place using the HAM-A and HAM-D at the end of weeks 1, 3, and 5. 🟢	Random allocation unclear. Company has provided further information on randomisation and blinding. Detail in paper, page 173 'The participants were randomized into two groups; an active CES group and a sham CES group'. However study record (NCT01533415) states non-randomised. ITT not used; for the intervention 5% and for the control 7% were lost to follow-up due to lack of compliance/study fidelity and not included in analysis. No information provided as to who conducted assessments. Not explicit if assessors blind. Clinically relevant change in score not described, rather Cohen's d effective size of 0.5 used in sample size calculation.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Lu & Hu (2014) China n=120	**Design:** Open label, randomised controlled trial. **Intervention:** Alpha-Stim SCS device for 6 weeks, once a day, for 60 continuous minutes, for a total of 42 treatments. At the initial visit the investigator set the sensory threshold. The intervention group was treated with paroxetine (10-20 mg/d) in combination with CES therapy (n=60). **Control:** Paroxetine (10-20 mg/d) (n=60) **Funding:** Not reported. **Status:** Published ●	**Participants:** Adults with diagnosis of anxiety disorder. **Setting:** Inpatient or outpatient departments of a mental health centre. Author affiliation is in China but setting not reported. ●	**Primary:** HAM-A reductive ratio was the indicator for efficacy evaluation. HAM-A reductive ratio ≥75% is clinically cured, 50% - 74% obviously improved, 25% - 49% improved, and <25% ineffective. Significant efficacy rate = [(number of cured cases + number of obviously improved cases)/ total number]×100%.. **Secondary:** CGI-SI was the secondary indicator for efficacy evaluation. WHO quality of life measurement table was used for assessment of quality of life. **Follow-up:** HAM-A was assessed in Weeks 0, 2, 4 and 6, and CGI-SI and WHOQOL-BREF was assessed in Weeks 0 and 6. ●	Open label, at risk of bias as patients assess their own symptoms. ITT analysis used (no loss to follow-up). Unclear if assessors were aware of intervention received by participants. No protocol record and not registered in trial database. Paroxetine is a SSRI which is in line with NICE pathway for GAD (although NICE recommends sertraline as first line treatment). BNF dose is 20 mg daily for GAD and SAD. Source of funding not reported.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Non-comparative studies (before and after design)				
Bystritsky et al. (2008) USA n=12	**Design:** Single-arm, open label pre-test post-test cohort pilot study. **Intervention:** Alpha-Stim SCS. At the initial visit the investigator set the sensory threshold, then the patient was instructed to self-administer consistently at home for 1 hour every day for a total of 6 weeks. **Control:** None **Funding:** Funding provided by Saban Family Foundation. The Alpha-Stim Stress Control System devices were loaned to the subjects free of charge by Electromedical Products International. **Status:** Published. 🟡	**Participants:** Adults with diagnosed GAD **Setting:** Patients recruited from UCLA Anxiety Disorders Program. Outpatient setting in the USA. 🟡	**Primary: C**hange in the HAM-A from baseline to 6 weeks. Response to treatment was defined as a reduction in ≥50% on HAM-A and a CGI-I score of 1 or 2. Symptom remission was CGI-I score of 1 or 2 and a score of ≤7 on HAM-A. **Secondary:** Assessments included Clinical Global Impressions-severity of illness (CGI-S) and CGI-I Improvement (beginning at week 2), and the HAM-D-17. Patients also completed the Patient Global Impressions-Improvement (PGI-I) scale and the Four-Dimensional Anxiety and Depression Scale (FDADS). **Follow-up:** Study visits were conducted at baseline and at the end of 3 and 6 weeks of treatment. 🟢	No control group. At risk of bias as patients assess their own symptoms. Small sample size (pilot study). 9 patients (75%) completed the study. 25% loss to follow-up. ITT analysis using last observation carried forward.

Morris et al. (2019) UK n=161	**Design:** Single-arm, open-label, consecutive, pre-test post-test cohort study with economic evaluation. **Intervention:** (n=161) Alpha-Stim AID. Participants offered 60 min/day, 100 μA per day, 6 consecutive weeks. Device not locked. Participants could choose to continue treatment for 6 weeks (12 weeks total). If participants started iCBT during the 6–12 weeks of Alpha-Stim, they could continue with Alpha-Stim while receiving iCBT. GPs could independently decide to place the patient on medication for GAD at the same time as participants continued to receive Alpha-Stim. **Control:** None **Funding:** Electromedical Products International (but had no role in design, conduct, reporting). **Status:** Published study.	**Participants:** Treatment seeking patients with GAD diagnosis who had not responded to computerised CBT or bibliotherapy over 24 weeks, and were waiting for iCBT for GAD (n=161 enrolled). GAD in combination with a comorbid depression or other anxiety disorder allowed. **Setting:** 2 NHS Improving Access to Psychological Treatment (IAPT) services in England.	**Primary:** Proportion of participants who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7. **Secondary:** Personal Health Questionnaire (PHQ-9) at 12 and 24 weeks, Athens Insomnia Scale (AIS) at 12 and 24 weeks, Work and Social Adjustment Scale (WASA) at 12 and 24 weeks, EQ5D-5L at 12 and 24 weeks. Other key outcomes are the proportion of cases who meet a clinically important ("reliable improvement") 5 point improvement on the GAD-7 at 12 and 24 weeks, the proportion who meet criteria for recovery (GAD-7 score of 7 or less and also exhibiting a 5 point drop in GAD-7 score) at 12 and 24 weeks, and the effect size of the change in GAD-7 score over 12–24 weeks. **Follow-up:** Clinical outcome and QoL measure were collected at 4, 6, 8, 12 and 24 weeks by e-mail, telephone or post according to participant preference.	No control group (before-after design). Open label, at risk of bias as patients assess their own symptoms. GAD-7 questionnaire self-administered. Large number of patients (78%) declined to participate. 30% withdrew from treatment at 12 weeks. 50% withdrew from follow-up. Missing completely at random (MCAR) assumption used and data imputed. ITT analysis used. Difficult to know how many patients completed each questionnaire because data imputed. Patient who started iCBT during Alpha-Stim treatment could receive both (80 patients (50%) had iCBT, although later the authors say 25 patients had CES & iCBT). Funded by company.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Overcash (1999) USA n=197	**Design:** Retrospective, open-label, pre-test post-test comparison cohort. No ethical approval described. **Intervention:** Alpha-Stim CES was used for about half the sessions (25 minutes) at a 0.05Hz frequency and a comfortable current setting up to 500 μA. Often patients were placed in a "Relax and Learn Room" where they watched videotapes of relaxing scenery and listened to superlearning music. Over 80% of the time patients were loaned an Alpha-Stim to take home and use once or twice a day in a manner consistent with how they were using it successfully in the clinic. **Control:** None. **Funding:** Not reported. **Status:** Published ●	**Participants:** Patients diagnosed with anxiety disorder and treated at author's clinic. Most patients reported very high levels of anxiety for past 2 months. All but 6 patients were referred by local physicians in the area (n=197 began treatment, 182 completed treatment). **Setting:** Outpatient private practice in the US. ●	Subjective self-rating of anxiety symptoms (0-100). Electromylegram (EMG) Electrodermal response (EDR) Peripheral temperature. **Follow-up:** Psychophysiological and subjective measurements of anxiety were made before and after treatment. Length of treatment not reported ●	Retrospective study with no control group. Open label, at risk of bias as patients assess their own symptoms. Eligibility criteria not described. No sample size calculation. Subjective and non-validated self-reporting outcome measure. Variable intervention and used alongside other non-study interventions. 92% of participants completed study. No ITT analysis. Funding source not reported.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Unpublished studies				
Voris (1995) **UNPUBLISHED** USA n=105 (60 with anxiety scores)	**Design:** Triple blind randomised controlled study. **Intervention:** Alpha-Stim 100 at 300 µA and 0.5 Hz for 20 minutes during regular therapy group (number of treatments not reported, description of usual therapy not given) (n=38; 31 with STAI score). **Controls:** Sham device (n=14 with STAI score) or no treatment (n=15 with STAI score). **Funding:** Not reported. **Status:** Unpublihsed ●	**Participants:** Individuals drawn from a general psychiatric population suffering from a clinically significant anxiety dysfunction (incl. agoraphobia, GAD, panic attacks, OCD, asocial phobia, simple phobia). **Setting:** Delos Mind/Body Institute, USA ●	**Outcomes:** State Trait Anxiety Inventory (STAI) EMG Skin temperature **Follow-up:** Not reported. Report says that over a period 10 days all of the groups that worked with stress or anxiety were tested. Measurements were recorded before and immediately following treatment. ●	Non-peer reviewed report (available on company website). Unclear description of population. Eligibility criteria not described. Inclusion of data from patients without diagnosed anxiety disorder. Active group included patients with manic-depression, psychosis, major depression, all of which demonstrated significant anxiety. These conditions are out of scope, therefore the generalisability of the results may be limited. No sample size calculation. Randomisation based on seats in therapy room (not truly random as element of patient self-selection). Number of Alpha-Stim treatments given not reported. (Information from the company suggests that outcomes were measured after a single Alpha-Stim session). Description of usual therapy not given. Only 60 of 105 randomised participants were included in the analysis because patients who did not meet anxiety criteria based on pre-treatment STAI scores were excluded during analysis of the data. Funding source not reported.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Green, amber, red colour coding indicates whether the study matches the scope of the assessment fully, partially, or not at all, respectively.				

Table 2 – Methodology of 7 studies excluded by EAC but which have outcomes relevant to the decision problem

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Chen et al. (2007) Location not reported (assumed to be China)	**Design:** Non-randomised, controlled study (blinding not fully reported). **Intervention:** Alpha-Stim 100, current intensity 100-500 μA, frequency 0.5 Hz. Each course was for 5 days, once a day for 10-15 mins, then 2 rest days. 3 courses total (n=30). **Control:** Sham device with no power (n=30).	**Participants:** Children at the age of 8 to 16 with mixed anxiety and depressive disorder (MAD). **Setting:** Psychological health clinic of hospital	Zung Self-Rating Depression Scale (SDS) Zung Self-Rating Anxiety Scale (SAS) EEG	**Out of scope based on population.** Patients with MAD which is out of scope because ICD-11 categorises MAD as a 'depressive disorder' not an 'anxiety or fear related disorder'. Inclusion criteria for study included, "diagnostic criteria for anxiety or depressive disorder were not satisfied. ***Key findings presented in section 5.***
Gibson & O'Hair (1987) USA	**Design:** 4-arm comparative study (blinding unclear) **Intervention:** Group 1) Alpha-Stim 350 at 0.5 Hz frequency and 50 μA. Duration and frequency not reported (with and without relaxation instructions) (n=16). Group 2) Relaxation instructions. Group 3) Alpha-Stim and relaxation instructions. **Control:** Electrodes with device turned off plus neutral tape (n=16).	**Participants:** Non-paid volunteers responding to newspaper advert. Subjects scoring ≥50 on state anxiety scale were considered anxious and included. **Setting:** Not reported.	State anxiety scale EMG scores	**Out of scope based on population.** No diagnosis of anxiety disorder. ***Key findings presented in section 5.***

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Kirsch et al. (2014) USA	**Design:** Retrospective cross-sectional, survey. **Intervention:** Alpha-Stim (model not reported) for minimum 20-60 minutes daily (n=152 responders). **Control:** None 🟡	**Participants:** Active duty service members and veterans who obtained an Alpha-Stim device through the US Department of Defense or Veterans Affairs medical centres and were using Alpha-Stim device for anxiety. No diagnosis of anxiety reported. **Setting:** Invited to participate in a web-based survey via email. 🔴	Questionnaire contained 27 questions covering medication use, activity, rating the effectiveness of CES technology for treating anxiety, PTSD, insomnia, and depression. 🟡	**Out of scope based on population.** No diagnosis of anxiety disorder. ***Key findings presented in section 5.***
Koleoso et al. (2013) Nigeria	**Design:** Prospective, controlled study with random allocation (3 groups plus control) **Intervention:** Group 1) Alpha-Stim 100 device, 45 minutes treatment in each session, 100-600 μA, 0.5 Hz, 3 days. Group 2) relaxation group therapy. Group 3) Alpha-Stim and relaxation group therapy (n=40 in total) **Control:** No treatment 🟢	**Participants:** Respondents who were experiencing oral pain conditions for ≥3 months and scored high on dental anxiety scale. **Setting:** Dental Centre of University of Benin, Nigeria. 🔴	Modified Dental Anxiety Scale (MDAS) 🟡	**Out of scope based on population.** Participants had diagnosis of dental pain and dental anxiety, but not an anxiety disorder. ***Key findings presented in section 5.***
Libretto et al. (2015) USA	**Design:** Retrospective, single arm cohort study. **Intervention:** CES (Alpha-Stim model not reported) as part of "trauma-focused behavioural health techniques with complementary and alternative medicine (CAM) modalities including acupuncture, massage, Reiki, reflexology, and yoga" (n=764). **Control:** None 🟡	**Participants:** Active-duty soldiers with PTSD symptoms. **Setting:** An intensive outpatient behavioural health program at a US Army Medical Centre providing integrative care for active-duty service members for the treatment of PTSD symptoms. 🔴	Overall health outcomes (PTSD, depression, anxiety, pain, and resilience) 🟢	**Out of scope based on population.** DSM-V and ICD11 categorise PTSD as not an anxiety disorder. ***Key findings presented in section 5.***

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Winick et al. (1999) USA	**Design:** Double blind, random allocation **Intervention:** Alpha-Stim 100 used at maximum comfortable level at 0.5 Hz. Used for entire dental procedure (n=17) **Control:** Sham device (n=16) 🟢	**Participants:** Subjects selected from author's dental practice, and reported anxiety about dental procedure they were about to undergo. **Setting:** Dental practice in US 🔴	Self-rated anxiety scales. 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder.
Yennurajalingam et al. (2018) USA	**Design:** Single-arm, open-label, cohort study. **Intervention:** Alpha-Stim M for 60 mins daily for 4 weeks (100 µA, 0.5 Hz). (n=33) **Control:** None 🟡	**Participants:** Advanced cancer patients with one or more of the four symptoms (depression, anxiety, sleep disturbance, and pain) **Setting:** University of Texas MD Anderson Cancer Center (MDACC) 🔴	Edmonton Symptom Assessment Scale (ESAS), Hospital Anxiety and Depression Scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Brief Pain Inventory (BPI) short form, and National Comprehensive Cancer Network (NCCN) Distress Thermometer 🟢	**Out of scope based on population.** Patients with advanced cancer, who have symptoms of anxiety but no diagnosis of anxiety disorder required. ***Key findings presented in section 5.***
🟢🟡🔴 Green, amber, red colour coding indicates whether the study matches the scope of the assessment fully, partially, or not at all, respectively.				

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

The EAC has included 6 studies as key evidence to the decision problem (Table 1). Two published RCTs (Barclay and Barclay, 2014; Lu and Hu, 2014), 1 unpublished RCT (Voris 1995) and 3 published uncontrolled before and after studies (Bystritsky et al. 2008; Morriss et al. 2019; Overcash 1999) were included. Morriss et al. (2019) also includes an economic evaluation (see section 9 of the economic evidence section). All were full-text, published papers.

Only Morriss et al. (2019) uses the current model of the device, Alpha-Stim AID as the intervention, the others use older models. Four of the studies used Alpha-Stim daily for 60 minutes for 5-6 weeks. Overcash (1999) used Alpha-Stim variably alongside other non-study interventions (relaxation techniques) and did not state a duration of treatment, and Voris et al (1995) which did not clearly report the number of Alpha-Stim treatments given but suggested that it was just a single 20 minute session alongside a usual therapy session. In Morriss et al. (2019), participants were given 6 weeks of Alpha-Stim treatment, and could then choose to have a further 6 weeks of treatment (12 weeks total).

Lu & Hu (2014) compares Alpha-Stim plus paroxetine (a SSRI drug used to treat anxiety disorders) to paroxetine alone. Barclay & Barclay (2014) compares Alpha-Stim to a sham device. Voris (1995) compares Alpha-Stim to 2 control groups: a sham device and a no treatment group.

The studies have sample sizes ranging from 12 (Bystritsky et al. 2008) to 197 (Overcash, 1999).

Five of the 6 studies used validated measures of anxiety symptoms (details in table 3). These were the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), a 14-item clinical interview assessment tool, GAD-7 (Spitzer et al. 2006), a 7-item, patient-rated measure of anxiety, the Four-Dimensional Anxiety and Depression Scale anxiety subscale (FDADS-anxiety), a 40-item

patient-rated measure of anxiety and depression, the State/Trait Anxiety Inventory (STAI) which is a 20 item questionnaire (Spielberger et al. 1983). Overcash (1999) used a non-validated self-rating of 0 to 100. Length of follow ranged from 5 to 24 weeks (Table 3).

Three studies used validated measures of depression symptoms (Table 3) which were the 17-item, clinician-administered Hamilton Depression Rating Scale (HAM-$D_{17;}$ Hamilton, 1960) or the 9-item Patient Health Questionnaire (PHQ-9) which is a self-administered depression module of the PRIME-MD diagnostic instrument for common mental disorders (Kroenke et al. 2001). Quality of life outcomes were reported in two studies (Table 3).

Table 3 – Summary of outcome measures used in the 6 included studies.

	Anxiety scale (reported time points, primary/main in bold)					**Depression scale (time points)**		**Other outcomes**
	HAM-A	**FDADS-anxiety**	**GAD-7**	**STAI**	**Non-validated 0-100 scale**	**HAM-D17**	**PHQ-9**	
Barclay (2014)	✓ (1,3,**5** weeks)					✓ (1,3,**5** weeks)		None
Lu & Hu (2014)	✓ (2,4,**6** weeks)							CGI-SI, WHOQOL-BREF
Bystritsky (2008)	✓ (**6** weeks)	✓ (**6** weeks)				✓ (**6** weeks)		None
Morriss (2019)			✓ (**12, 24** weeks)				✓ (**12, 24** weeks)	AIS, WASA, EQ-5D-5L
Overcash (1999)					✓ (NR)			None in scope
Voris (1995)				✓ After treatment				

AIS; Athens Insomnia Scale; CGI-SI: Clinical Global Impression severity of illness; FDADS: Four Dimensional Anxiety and Depression Scale; GAD-7: General Anxiety Disorder-7; HAM-A: Hamilton Anxiety rating scale; HAM-D17: Hamilton Depression rating scale; iCBT; individual Cognitive Behavioral Therapy; PHQ-9: Patient Health Questionnaire-9; STAI: State/Trait Anxiety Inventory; WSAS: Work and Social Adjustment Scale; WHOQOL-BREF: World Health Organization Quality of Life

All studies included adults with a primary diagnosis of an anxiety disorder except Voris et al. (1995) which had an unclear description of the population. Participants were selected for the general psychiatric population in a clinic

and reported anxiety or high stress in their intake interview; they had manic-depression, psychosis, major depression with significant anxiety. Morriss et al. (2019) specifically described the population as treatment-seeking patients with GAD diagnosis who had not responded to computerised CBT or bibliotherapy over 24 weeks, and were waiting for iCBT for GAD. In this study, the decision to commence iCBT was made independently of the study investigators; if participants started iCBT during the 6-12 weeks of Alpha-Stim treatment they could continue to use Alpha-Stim whilst receiving iCBT at the same time. None of the 6 studies reported whether participants had undergone previous psychological interventions such as CBT. Barclay & Barclay (2014) reported that the duration of medication use to treat mental health conditions was 17.2 years on average. Bystritsky et al (2008) reported that 41.7% of participants had been taking psychotropic medications for at least 3 months prior to enrolment and continued throughout the study. Overcash (1999) reported previous treatments: 26% of participants had used anxiolytic medications unsuccessfully, 16% had been placed on antidepressant medication, had used alcohol to self-medicate, had individual psychotherapy, or had behaviour modification therapy; and 58% had received no previous therapy for their anxiety disorder. The authors reported that many (no value given) patients had received psychological therapies such as individual or group therapy, alcohol treatment, or behaviour modification prior to treatment with Alpha-Stim.

In three of the studies (Barclay & Barclay, 2014; Bystritsky et al. 2008; Morriss et al. 2019), participants were permitted to take medication to treat their anxiety alongside the study treatment. In Lu & Hu (2014) participants only had paroxetine as a study treatment alongside Alpha-Stim. Overcash (1999) reported that 26% of participants were on anxiolytics when Alpha-Stim treatment began, 16% were on other medication (mostly antidepressants), 4% were on anxiolytics and antidepressants, and 54% were not on any medication when they began treatment.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The company submission does not include a formal critical appraisal of the studies included in the clinical evidence review. There is no mention of the use of any checklist for appraising study quality. The company briefly highlights the limitations of Alpha-Stim studies in section 5 of their submission. No details of how those limitations were assessed or their impact on the quality of the clinical evidence has been presented. The EAC agrees with most of the limitations reported by the company, but considers their critical appraisal to be incomplete.

The EAC used two formal critical appraisal checklists to rate the strength of the 6 included studies (Appendix D). The Revised Cochrane risk-of-bias tool for randomized trials (RoB 2; Sterne et al. 2019) was used to appraise the three RCTs, and the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group tool (National Heart, Lung, and Blood Institute. 2014) was used for the non-comparative, before and after studies. No studies were at risk of patient overlap.

Two of the RCTs were found to be at high risk of bias (Barclay & Barclay 2014; Voris 1995) and the other had some concerns regarding the risk of bias (Lu & Hu, 2014). All three studies were rated as having "some concerns" around the randomisation process and deviations from the intended interventions. The published paper for Barclay & Barclay (2014) states that patients were randomised into 2 groups, there is no description of how an allocation sequence was generated and is not clear how patients were allocated to the two groups. Furthermore, the study record (NCT01533415) states that the study is non-randomised. The EAC contacted the study author who confirmed that the study was randomised and that "the company provided an equal number of devices of active and sham. As people came in, they were provided a device". The company also provided the following information: "The study was a true double-blind RCT. When the research devices are programmed for active and sham conditions for an RCT by EPI (the manufacturer), they are placed in the shipping container randomly. Investigators distribute devices to participants with no knowledge of which

devices are active and which are sham. This protocol ensures double-blinding integrity, as neither investigator nor participants knows the condition of the device." Also in this study there was a high risk of bias in the measurement of outcomes because no information was provided as to who conducted assessments or whether they were blinded (although the above information provided by the company states that investigators were blinded). In Lu & Hu (2014), there was some concerns around the risk of bias of the reported results because there was no published protocol or clinical trial database entry. In Voris (1995) there was a high risk of bias in the category of missing data because it was not reported how many participants were randomised to each of the 3 groups and only 60 of 105 randomised participants were included in the analysis.

The three non-comparative, observational studies were rated as poor quality and were at risk of bias. In Morriss et al. (2019) a large number of potential participants (78%) identified through the IAPT database declined to take part (reasons not given). One hundred and twelve participants (69.9%) completed at least 6 weeks of treatment; of the 30.4% who withdrew from treatment by 12 weeks nine (5.6%) could not find the time to complete the treatment, four (2.5%) withdrew because of no improvement, four (2.5%) withdrew because of side effects (two with headaches and insomnia, one with nausea and one with a strange feeling after use), two (1.2%) withdrew because they felt better, and 30 (18.6%) gave no reason. A high number of participants (50%) withdrew from follow-up at 12 weeks. Missing data were imputed following a test to show adherence to missing completely at random (MCAR), but this is a large proportion of data to impute and may be unreliable. Bystritsky et al (2008) had the issue of a small sample size, only 9 of 12 patients completed the study, and last observation carried forward was used to impute missing data.

Overcash (1999) was particularly problematic because it did not report eligibility criteria, there was no sample size calculation, the self-rating anxiety score was non-validated, and the analysis was not intention to treat (ITT). Furthermore the intervention was unclear, variable and was combined with

other non-study treatments including videos of relaxing scenery and superlearning music (a technique where music is played to establish an environment conducive to learning).

5.3 *Results from the evidence base*

Six studies met NICE's scope and have been included as key evidence by the EAC. There were 2 published, comparative studies (Barclay & Barclay 2014; Lu & Hu 2014), 1 unpublished comparative study (Voris 1995), and 3 non-comparative studies (Bystritsky et al. 2008; Morriss et al. 2019; Overcash 1999). Results, as well as key sources of variation between the studies (population, version of the device, control group), are displayed in table 4.

Anxiety scores

All 6 included studies used measures of anxiety symptoms before and after treatment with Alpha-Stim (Tables 3 and 4). The HAM-A questionnaire was used in 3 studies (Barclay & Barclay 2014; Lu & Hu 2014; Bystritsky et al. 2008). In Barclay & Barclay (2014) the Alpha-Stim group reported a significantly greater mean reduction in HAM-A scores from baseline to week 5 (32.8%) than the sham device group (9.1%, p=0.001) (although these values appear to be from week 1 to week 5, not baseline as is described in the paper). 83% of patients in the Alpha-Stim group reported a ≥50% reduction in HAM-A scores (number in control group not reported). In Lu & Hu (2014), HAM-A scores significantly reduced ($p<0.05$) in both groups from baseline to week 6 (Alpha-Stim plus paroxetine group changed from a mean of 25.0 ±4.2 to 8.3 ±3.7, and the paroxetine only control group reduced from 24.5 ±4.3 to 12.4 ±3.5). The authors report that the difference between the groups was significantly different ($p<0.01$). A threshold of a reduction in HAM-A scores of at least 75% was considered "clinically cured", between 50 and 74% reduction was "obvious improvement", between 25 and 49% was "improvement" and less than 25% was deemed "ineffective". The study found that in the Alpha-Stim group 18 cases were cured (30%), 28 cases were obviously improved (47%), 10 cases were improved (17%), and 4 cases were ineffective (7%). In the control group, the corresponding cases were 14 (23%), 18 (30%), 16 (27%) and 12 (20%) respectively. The authors reported a significant efficacy

rate which was the combined proportions of cured and obviously improved participants. In the Alpha-Stim and control groups the significant efficacy rates were 76.7% and 53.3%, respectively, which were significantly different ($p<0.05$). The single arm study Bystritsky et al. (2008), the mean HAM-A scores decreased significantly from baseline to 6 weeks (a change from 21.3 to 12.7; $p=0.01$).

One study (Morriss et al. 2019) used the GAD-7 scale as a self-reported anxiety measure. This single arm study showed a significant drop in mean GAD-7 scores from 15.8 at baseline to 8.9 by 12 weeks and this was maintained to 9.0 at 24 weeks ($p < 0.001$). Seventy-two (44.7%) participants achieved remission and recovery on the GAD-7 at 12 weeks (n=81) and 77 (47.8%) at 24 weeks (n=72). The authors report that the majority of the improvement in anxiety symptoms were achieved in the first 6 weeks.

Overcash (1999) reported a significant reduction in mean anxiety scores (non-validated 0-100 scale) of 27.5 points ($p<0.05$) from pre-treatment to post treatment (time points not reported).

The unpublished RCT by Voris (1995) reported significant improvements in anxiety scores (STAI questionnaire) following treatment with Alpha-Stim compared to both the sham device ($p=0.0001$) and no treatment group ($p=0.0001$). Although not clearly described it appears that patients had a single 20 minute Alpha-Stim treatment alongside their usual therapy session.

Self-reported depression

Three of the 6 included studies used validated, self-reported depression measures (Barclay & Barclay, 2014; Bystritsky et al. 2008; Morriss et al. 2019). Barclay & Barclay (2014) reported a 32.9% reduction from week 1 (reported as baseline in the study) to week 5 in HAM-D_{17} scores in the Alpha-Stim group compared to 2.6% in the control group ($p=0.001$). The study reports that 82% of the Alpha-Stim group had a decrease of ≥50% in depression scores ($p<0.001$) from baseline to week 5 (not reported for control group). Bystritsky et al. (2008) reported that HAM-D_{17} scores reduced significantly from 10.5 at baseline to 6.0 at 6 weeks ($p=0.01$). Morriss et al

(2019) reported a reduction in PHQ-9 scores from 16.1 at baseline to 8.9 and 10.4 at 12 and 24 weeks, respectively. Differences in PHQ-9 scores were only significant between baseline and 12 weeks and not 24 weeks.

Insomnia

One study (Morriss et al. 2019) reported outcomes relating to insomnia. AIS scores reduced from 12.9 at baseline to 9.9 and 7.9 at 12 and 24 weeks, respectively. The authors report that there was a significant reduction in AIS scores over the 24 week period ($p<0.001$), and that 24.2% and 28.0% of participants achieved remission on the AIS measure at 12 and 24 weeks, respectively, with a small effect size.

Quality of life

Two studies (Lu & Hu 2014; Morriss et al. 2019) reported outcomes relating to insomnia. EQ-5D-5L scores improved from 51.6 at baseline to 64.8 at 12 weeks, and 62.5 at 24 weeks, which was significant over the 24 weeks ($p<0.0001$) but the effect size is small (Morriss et al. 2019). Lu & Hu (2014) reported that differences in scores in each domain of the WHOQOL-BREF tool between the intervention and control groups were not statistically significant. Only the difference in scores in the physical domain of the tool was statistically significant between the control and intervention groups ($P<0.05$).

Work and social functioning

One study (Morriss et al. 2019) reported outcomes relating to work and social functioning. Using the WASA outcome measure, there was an improvement (reduction) in scores from 20.8 at baseline to 14.9 at 12 weeks and 16.0 at 24 weeks. The effect was significant over the 24 weeks but the effect was small. The authors reported that 17.4% and 18.0% reached normal function at 12 and 24 weeks respectively.

Severity of illness

One study (LU & Hu, 2014) reported outcomes relating to global severity of illness. CGI-SI scores of the two groups significantly decreased over 6 weeks,

however the decrease in CGI-SI scores of the Alpha-Stim group was more significant than that of the control group, and the difference was statistically significant ($P<0.05$).

Table 4 – Results form 6 studies included by the EAC

Study	Population (P), intervention (I), comparator (C)	Anxiety scores	Depression scores	Other outcomes
Comparative studies				
Barclay & Barclay (2014)	P: Adults with primary diagnosis of anxiety I: Alpha-Stim 100 C: Sham device	**Anxiety score (HAM-A) at 5 weeks** • Intervention group had lower anxiety scores than the control group (n=51) from baseline to week 5 (F=43.4, p=0.001, d=0.94). Values appear to be from week 1 to 5, not form baseline as described in paper text. • 83% of intervention group had decrease of ≥50% in anxiety scores (p<0.001) from baseline to week 5. • HAM-A decrease in the intervention group was 32.8% (19.89-13.37), and for the control group it was 9.1% (21.98-19.98) by week 5 (values appear to be from week 1 to 5, not form baseline as described in paper text).	**Depression score (HAM-D_{17}) at 5 weeks** • Intervention group (n=57) had lower depression scores than the control group (n=51) from baseline to week 5 (F=17.1, p=0.001, d=0.78). Values appear to be from week 1 to 5, not form baseline as described in paper text. • 82% of the intervention group had a decrease of ≥50% in depression scores (p<0.001) from baseline to week 5. • HAM-D mean decrease was 32.9% (9.64-6.47) for the intervention group and 2.6% (10.22-9.96) for the control group from baseline to week 5 (values appear to be from week 1 to 5, not form baseline as described in paper text).	None
Lu & Hu (2014)	P: Adults with diagnosis of anxiety disorder	**Anxiety score (HAM-A) at 6 weeks** • In the intervention group the HAM-A score reduced from 25.0 (sd 4.2)		**Severity of illness (CGI-SI)** • CGI-SI scores significantly decreased in both groups

	I: Alpha-Stim SCS & paroxetine (10-20 mg/d) C: Paroxetine (10-20 mg/d)	before treatment to 8.3 (sd 3.7) at week 6. In the control group the HAM-A score reduced from 24.5 (sd 4.3) before treatment to 12.4 (sd 3.5) at 6 weeks after treatment. The difference between the arms was significantly different (p<0.01). **Clinical efficacy** • In the CES study group (n=60), 18 cases were cured (30%), 28 cases were obviously improved (47%), 10 cases were improved (17%), and 4 cases were ineffective (7%). Significant efficacy rate was 76.67%. • In the control group, the corresponding cases were 14 (23%), 18 (30%), 16 (27%) and 12 (20%) respectively, with the significant efficacy rate 53.33%. There was statistically significant difference in the significant efficacy rate between the two groups ($\chi 2=4.62$, P<0.05).		(P<0.05), however the CES study group was more significant than that of the control group, and the difference was statistically significant (P<0.05). **Quality of life (WHOQOL-BREF)** • Differences in scores between groups in each domain were not statistically significant. • Before and after differences in QOL scores were significantly different across all domains at week 6 (p<0.05) (not between groups) • Only the difference in scores in the physical domain was statistically significant between the control and intervention groups (P<0.05).
Study	**Population (P), intervention (I), comparator (C)**	**Anxiety scores**	**Depression scores**	**Other outcomes**
Non-comparative studies				
Bystritsky et al. (2008)	P: Patients with diagnosed GAD I: Alpha-Stim SCS C: None	**Anxiety score (HAM-A) at 6 weeks n=12** • Mean HAM-A scores decreased significantly from baseline (21.25 sd 5.82) to 6 weeks (12.67 sd 5.47) (p=0.01).	**Depression score (HAM-D_{17}) n=12** • HAM-D_{17} scores changed from 10.50 (sd 15.01) at baseline to 6.00 (sd 3.64) at 6 weeks (p=0.01).	None

		• At 6 weeks, 6 patients were classified as responders (50% decrease on HAM-A and score of 1 or 2 on the CGI-I). 2 patients met criteria for symptom remission (defined as CGI-I score of 1 or 2 and a score of ≤7 on HAM-A). **FDADS-Anxiety subscale n=12** • Change from baseline (30.58 sd 11.24) to 6 weeks (23.83 sd 7.57) in the FDADS-Anxiety subscale (p=0.039).		
Morriss et al. (2019)	P: Treatment seeking patients with diagnosed GAD awaiting iCBT I: Alpha-Stim AID C: None Analysis based on n=161 missing data imputed.	**Anxiety score (GAD-7) at 12 & 24 weeks** • 72 (44.7%) participants achieved remission and recovery on the GAD-7 at 12 weeks (n=81) and 77 (47.8%) at 24 weeks (n=72). • The proportions of participants achieving reliable improvement on the GAD-7 were 102 (63.4%) and 105 (65.2%) at 12 and 24 weeks respectively. No patient showed reliable deterioration at 12 or 24 weeks. • GAD-7 score reduced from mean (sd) 15.77 (3.21) to 8.92 (5.42) by 12 weeks and this was maintained to 8.99 (6.18) at 24 weeks (F = 72.02, p < 0.001). • Of the 81 participants who only received CES, 49 (60.3%) achieved remission on the GAD-7 at 12 weeks and 53 (65.4%) achieved remission on the GAD-7 at 24 weeks.	**Depression score (PHQ-9) at 12 & 24 weeks** • 45.3% and 50.9% of participants achieved remission on PHQ-9 score at 12 (n=81) and 24 weeks (n=72), respectively. • Mean score reduced from 16.07 at baseline to 8.91 (significant) and 10.42 (n.s.) at 12 and 24 weeks, respectively. • The effect size was small (partial Eta square = 0.21). • There was some worsening of depression symptoms by week 24	**Insomnia (AIS)** • 24.2% and 28.0% achieved remission on the Athens Insomnia Scale at 12 (n=81) and 24 weeks (n=72) respectively. • There was a statistically significant within-subjects drop in insomnia over the 24 week period (F=42.69, df1=5.0/df=542.9, p < 0.001) and the effect size was medium (partial Eta square = 0.21). **Work and social function (WSAS)** • 17.4% and 18.0% reached normal function at 12 (n=81) and 24 weeks (n=72) respectively. • There was a significant within-subjects effect of Alpha-Stim over the 24 weeks (F=17.35, p < 0.001) but the effect size is small (partial Eta square=0.10).

		• Of the 25 participants who received both CES and iCBT, 17 (68%) achieved remission and recovery on the GAD-7 and 23 (92%) achieved reliable improvement at 12 and 24 weeks.		**Quality of life (EQ-5D-5L) n=161** • There was an improvement from 51.61 at baseline to 64.80 at 12 weeks, and 62.50 at 24 weeks. • There was a significant within-subjects effect of Alpha-Stim CES over the 24 weeks (F=13.94, p < 0.0001) but the effect size is small (partial Eta square=0.08).
Overcash (1999)	P: Patients diagnosed with anxiety disorder I: Alpha-Stim CES C: None	**Subjective anxiety scale n=182** • Mean difference from pre-treatment to post-treatment of 27.5 (sd 16.3) p<0.05 (time points not reported)		• Electromylegram, Electrodermal response, and temperature were reported by the authors but the EAC consider these outcomes to be out of scope.
Unpublished study				
Voris (1995)	P: Patients reporting anxiety and stress I: Alpha-Stim 100 C: Sham device or no treatment	**STAI (n=60)** • STAI scores reduced from 50 (sd 8.1) to 34 (sd 7.4) in the active group (n=31), 51 (sd 8.6) to 50 (sd 8.5) in the sham device group (n=14), and there was no change in the control group 48 (sd 6.0) to 48 (8.8) (n=15) . Differences between the active and control groups, and between the active and placebo groups was significant (p=0.001 in both cases). There was no significant difference between the control groups (p=0.3902).		• Electromylegram and temperature were reported by the authors but the EAC consider these outcomes to be out of scope.

AIS; Athens Insomnia Scale CES; CGI-SI: Clinical Global Impression severity of illness; FDADS: Four Dimensional Anxiety and Depression Scale; GAD-7: General Anxiety Disorder-7; HAM-A: Hamilton Anxiety rating scale; HAM-D17: Hamilton Depression rating scale; iCBT; individual Cognitive Behavioral Therapy; PHQ-9: Patient Health Questionnaire-9; STAI: State Trait Anxiety Inventory; WSAS: Work and Social Adjustment Scale; WHOQOL-BREF: World Health Organization Quality of Life.

5.4 *Results of studies excluded by EAC with outcomes relevant to the decision problem*

Seven studies were excluded by the EAC but contained potentially relevant information on the effect of Alpha-Stim on anxiety symptoms (Chen et al. 2007; Gibson & O'Hair 1987; Kirsch et al 2014; Koleoso et al. 2013; Libretto et al. 2015; Winnick et al 1999; Yennurajalingam et al. 2018) (Table 5). The populations of these studies were varied and included: children with a diagnosis of mixed anxiety-depressive disorder (Chen et al. 2007), adult volunteers responding to an advert with anxiety score 50 or over (Gibson & O'Hair 1987), service members with anxiety symptoms (Kirsch et al. 2014), active duty personnel with PTSD (Libretto et al. 2015), adults with dental anxiety (Koleoso et al. 2013; Winick et al. 1999), and patients with advanced cancer and anxiety symptoms (Yennurajalingam et al. 2018).

Four studies were comparative, of which two reported some form of random allocation of participants (Koleoso et al. 2013; Winick et al. 1999), and two were non-randomised studies (Chen et al. 2007; Gibson & O'Hair 1987). The remaining 3 were uncontrolled studies (Kirsch et al 2014; Libretto et al. 2015; Yennurajalingam et al. 2018), of which 2 were retrospective. Six of the 7 studies used validated, self-reported measures of anxiety. Two used non-validated scales (Kirsch et al. 2014; Winick et al. 1999) (Table 5).

All four comparative studies reported significantly reduced anxiety symptoms when treated with Alpha-Stim compared to the control group (Table 5). Two of the three non-comparative studies reported significant improvement in anxiety symptoms after treatment with Alpha-Stim (the third study did not carry out a statistical comparison).

Table 5 - Results from 7 excluded studies with outcomes relevant to the decision problem

Study name	Study details	Key findings relating to anxiety	EAC comments
Comparative studies			
Chen (2007)	Non-randomised, controlled study. Children (aged 8-16) with MAD treated with Alpha-Stim (n=30) vs sham device (n=30).	Control group reduced SAS score from 46.0 to 39.2, intervention group was 48.3 before treatment and 29.7 after treatment. The effect of the treatment was significant (p<0.01).	MAD is depressive disorder' not an 'anxiety or fear related disorder'. SAS is a validated anxiety measure. This study is out of scope.
Gibson & O'Hair (1987)	Non-randomised, controlled study. Non-paid volunteers responding to newspaper advert. Subjects scoring ≥50 on state anxiety scale were included. Patients treated with Alpha-Stim (n=16) or sham device (n=16).	There was a reduction in STAI score of 22.25 in the intervention group (Alpha-Stim only) and 1.31 in the control group (p<0.01).	Random allocation not described. Blinding not clearly described. Duration and frequency of intervention not reported. STAI is a validated measure. This study is out of scope.
Koleoso (2013)	Randomised controlled study. Adults experiencing oral pain conditions for ≥3 months and scored high on dental anxiety scale. 40 participants completed 3 treatment sessions. Groups were: control (n=10), relaxation (n=10); CES (n=10), CES & relaxation (n=10).	CES significantly reduced dental anxiety (control 18.30 vs Alpha-Stim 10.20; p< .05). Alpha-Stim no better than relaxation therapy.	Random allocation not described. Appears to be open label but not clear. Details of interventions not clear. Outcome measure was a validated tool specific to dental anxiety. Results from anxious dental patients may be of limited generalisability to patients with anxiety disorder diagnosis. This study is out of scope.
Winick (1999)	Double blind, random allocation. Patients reporting anxiety about upcoming dental procedure, treated during dental procedure with Alpha-Stim (n=17) or sham device (n=16).	Anxiety score reported by the patient after the procedure on a VAS reduced by -30.1 (SE 9.0) in the treatment group and -4.2 (SE 3.9) for sham device (p<0.02). Patients also reported a larger reduction in anxiety on a Likert scale in the active group (4.8 SE 0.4) compared to the control group (2.5, SE 0.3) p<0.01.	Allocation not truly random. Unclear how researchers were blinded. Likert scale not validated (5 of 7 responses were positive direction). Differences between groups in type of procedure. Results from anxious dental patients may be of limited generalisability to patients with anxiety disorder diagnosis. This study is out of scope.
Non-comparative studies			
Kirsch (2014)	Retrospective, single arm, cross-sectional, survey. Service members and veterans (n=114) who reported	34.1% and 9.1% of participants who used Alpha-Stim with medications reported moderate or marked improvement in perception of anxiety,	Non-validated outcome measure. Likert scale not validated (5 of 7 responses were positive direction). No statistical comparison.

	anxiety and who were given an Alpha-Stim device.	respectively. These values were 26.9% and 30.8% in participants who used Alpha-Stim alone.	This study is out of scope.
Libretto (2015)	Retrospective, single arm cohort study. Active duty personnel with moderate to severe PTSD (n=764). Intervention was Alpha-Stim as part of an integrative programme of treatments. No control.	Anxiety score (BAI) (n=567) reduced from 27.0 before treatment to 20.9 after (P<0.0001). Patient satisfaction (% rating of 4/5 or 5/5) ranged from 74% to 100% over 5 years.	Alpha-Stim delivered as part of wider programme of treatment. Validated anxiety outcome measure used. Results from patients with PTSD are out of scope and may be of limited generalisability.
Yennuraj alingam (2018)	Single-arm, open-label, cohort study. Patients with advanced cancer and one or more of the four symptoms (depression, anxiety, sleep disturbance, pain) (n=33 of 36 completed study).	56% and 28% of participants achieved 25% and 50% decrease in anxiety symptom intensity and distress (HADS). Median change of 2.5 points in the anxiety measure of HADS (p<0.001).	Results from anxious patients with advanced cancer may be of limited generalisability to patients with anxiety disorder diagnosis. This study is out of scope.
BAI: Beck Anxiety Inventory; HADS: hospital anxiety and depression scale; SAS: Zung Self-rating Anxiety Scale; STAI: state trait anxiety inventory; VAS: visual analogue scale			

6 Adverse events

The EAC searched the MHRA's field safety notices and medical device alerts, no adverse events were identified. The MAUDE (FDA) database was searched and 3 adverse events were identified, 2 of these were identified by the company, the other is as follows:

MAUDE Report MW5025466 stated that during treatment a patient was burned on both ears by the device that was used, the patient was using the device as prescribed and instructed. The company has stated that since this incident the earclips have been redesigned to minimize the risk of this effect.

The Alpha-Stim user manual states: No significant lasting side effects have been reported. Occasional headache, discomfort or skin irritation under the electrodes or lightheadedness may occur.

However the company do maintain records on adverse events reported both in clinical data and from customers; 56 were reported between 2012 and 2019. These included: skin irritation, leg pain, vasovagal response, dizziness/tinnitus, paradoxical reaction, headache, nausea, intestinal spasms/bloating and insomnia. The company state that when comparing the number of units sold to the number of reported adverse events, the ratio is 0.04%.

Only 2 studies (Bystritsky et al., 2008 and Morriss et al., 2019) included by the EAC reported adverse events (Appendix F), the extracted data matched with that of the company for the same studies. Barclay & Barclay (2014) stated that no participant reported any adverse events verbally or in their treatment log during the study. Neither Overcash (1999) or Lu and Hu (2014) reported if adverse events had occurred or not. The company included 10 additional studies for adverse event data; the EAC checked these publications for reported adverse events and agreed with the company's findings. The EAC is in agreement with the company that adverse events are rare and self-limiting; the EAC concludes that use of Alpha-Stim does not raise any safety concerns.

7 Evidence synthesis and meta-analysis

7.1 *Company's meta-analysis*

The company presented a new and unpublished meta-analysis on the effect of Alpha-Stim on anxiety in their submission. The meta-analysis included 10 RCTs which the company states were studies on anxiety. The company included a forest plot and summary statistics based on the standardized mean difference between study groups at post-test from the 10 included studies. Also presented is a summary of the meta-analysis summary statistics. Of the 10 studies included in the company's meta-analysis, only 3 are relevant to the decision problem of this topic (Barclay & Barclay, 2014; Lu & Hu, 2014; Voris 1995). The other 7 studies in the company's meta-analysis have been excluded by the EAC (see appendix G for further details on the EAC's critique of the company's meta-analysis). The EAC do not consider the results of the meta-analysis to be generalisable to a population with an anxiety disorder and therefore its results are not relevant to the decision problem.

7.2 *EAC's meta-analysis*

Only two published and one unpublished comparative studies are relevant to the current decision problem (Barclay & Barclay, 2014; Lu & Hu, 2014; Voris 1995) and these have important methodological differences. The EAC has not undertaken a new meta-analysis for this topic because of the limited evidence and heterogeneity between the two comparative studies included by the EAC. Key differences between the studies are as follows:

- **Setting:** Barclay & Barclay (2014) was in a primary care setting in the US, Voris (1995) was a clinic in the US, whilst Lu & Hu (2014) was carried out in inpatient or outpatient departments of a mental health centre in China.

- **Blinding:** Barclay & Barclay (2014) and Voris (1995) are blinded whilst Lu & Hu (2014) is open-label.

- **Intervention:** in Barclay & Barclay (2014) patients used the Alpha-Stim 100 for 1 hour daily for 5 weeks, in Lu & Hu (2014) patients used

Alpha-Stim SCS for 1 hour daily for 6 weeks in combination with paroxetine (10-20 mg/d), in Voris (1995) it appears that patients had one 20 minute Alpha-Stim treatment during their therapy session (number of treatments not clearly reported).

- **Control:** Barclay & Barclay (2014) and Voris (1995) used a sham device in the control group, Lu & Hu (2014) used paroxetine and no CES device in the control group.

- **Outcomes:** the study endpoint in Barclay & Barclay (2014) was HAM-A scores at 5 weeks (compared to week 1), whereas Lu & Hu (2014) used the same tool at 6 weeks (compared to week 0). Voris et al. (1995) used the STAI tool immendiately after treatment.

The EAC have presented the changes in anxiety symptom from the 6 included studies in table 6.

Table 6 - Anxiety scores and response rates from 6 studies included by the EAC

	Baseline anxiety score	Endpoint anxiety score	Difference in anxiety score & response rate	P-value
Comparative studies				
	HAM-A (sd)			
Barclay & Barclay (2014)	C=21.98 (NR) I=19.89 (NR) (week 1)	C=19.98 (NR) I=13.37 (NR) (week 5)	C=2.00 (9.1%) I=6.52 (32.8%) Response rates*: C= NR I= 83%	P=0.001
Lu & Hu (2014)	C=24.5 (4.3) I= 25.0 (4.2) (week 0)	C=12.4 (3.5) I=8.3 (3.7) (week 6)	C=16.7 (66.8%) I=12.1 (49.4%) Response rates*: C= 53.33% I= 76.67%	P<0.01
	STAI (sd)			
Voris (1995) Unpublished	Sham= 51 (8.6) No treatment= 48 (6.0) I= 50 (8.1)	Sham= 50 (8.5) No treatment= 48 (8.8) I=34 (7.4)	NR	P=0.001 for I vs both controls
Non-comparative studies				
	HAM-A (sd)			
Bystritsky et al. (2008)	21.25 (5.82)	12.67 (5.47)	Response rates: 50% ITT 67% completers	P=0.001
	GAD-7			
Morriss et al. (2019)	15.77 (3.21) (week 0)	8.92 (5.42) (week 12) 8.99 (6.18)	Remission rates (overall): 44.7% (week 12) 47.2% (week 24)	P=0.001

		(week 24)	Remission rates (Alpha-Stim only): 60.5% (week 12) 65.4% (week 24)	
	Subjective anxiety scale (0-100)			
Overcash (1999)	62.3 (NR)	14.8 (NR)	27.5 (sd 16.3)	P<0.05
*response defined as at least 50% reduction in HAM-A score C: control; I: intervention.				

8 Interpretation of the clinical evidence

Despite weaknesses in the evidence base, the EAC considers that the available evidence supports the short term clinical efficacy of Alpha-Stim as a treatment for generalised anxiety disorder. Adverse events from Alpha-Stim use are rare and self-limiting and the EAC concludes that use of Alpha-Stim does not raise any safety concerns.

A considerable amount of evidence was presented by the company, but the EAC have only considered the 6 studies (2 published RCTs, 1 unpublished RCT, and 3 non-comparative studies) which are relevant to the current decision problem. Three RCTs show statistically significant improvements in anxiety scores in adults treated with Alpha-Stim for generalised anxiety disorder above those of the control group (paroxetine, sham device, or no treatment). Three non-comparative studies also show significantly improved anxiety symptoms after treatment with Alpha-Stim. The small number of studies and heterogeneity in their design means that meta-analysis is not appropriate.

The EAC found the strength of the evidence to be limited. All three RCTs were at risk of bias and the three non-comparative studies were rated as poor quality. Only one study (non-comparative) was conducted in an NHS setting (Morriss et al. 2019). The absence of a control group and concurrent use of other therapies means that improvements in anxiety scores cannot be attributed to Alpha-Stim with any certainty. The remaining studies which are set outside the UK's NHS have more limited generalisability to the decision problem. However, it is reasonable to assume that the improvements in patients treated with Alpha-Stim compared to the control groups seen in comparative studies would be replicated in standard practice in the NHS. However, the effect size may be reduced in a real-life NHS setting as efficacy

trials can often overestimate an intervention's effect when implemented in clinical practice for reasons such as concomitant use of other therapies, differences in study sample versus larger population, patient adherence to treatment programme, and clinician preference. There is no evidence comparing Alpha-Stim directly to iCBT, therefore we cannot determine whether Alpha-Stim is more or less effective than current treatment. Morriss et al. (2019) references a remission rate for iCBT of 54.2% from a study by Gyani et al. (2013) which is slightly higher than the overall remission rate for Alpha-Stim of 44.7% and 47.8% at 12 and 24 weeks, respectively.

There is limited evidence on whether the effect of Alpha-Stim is maintained in the long term. The longest follow-up for Alpha-Stim as a treatment for generalised anxiety is 24 weeks in one study (Morriss et al. 2019). The remaining studies followed patients for 5 or 6 weeks. Morriss et al. (2019) reported that the reduction in anxiety symptoms were maintained at 24 weeks, but that the majority of effect is seen in the first 6 weeks.

There is no evidence on whether Alpha-Stim reduces the use of medication for anxiety and the available evidence does not support its use as a replacement for pharmaceutical therapy. Overcash (1999) comments that of the patients who were on medication when they started Alpha-Stim treatment (26% were on anxiolytics, 16% were on other medication including antidepressants, and 4% were on both anxiolytics and antidepressants), to the best of the investigator’s knowledge none of these patients were on medication when they left treatment successfully (successful treatment is not clearly defined). In 3 of the included studies patients were permitted to continue taking SSRI medication.

The high number (78%) of patients refusing to participate in Morriss et al. (2019) is important and indicates that some patients may not want to use the Alpha-Stim device; reasons for declining were not presented. The authors explain that invitation to the research study came through a cold call from the clinical team, and suggest that uptake might be higher if patients were prepared for Alpha-Stim as a treatment option through the IAPT service. Only one other study reported refusal rates (Barclay & Barclay 2014) and it was

much lower, 8% participation refusal. Patient attrition after starting treatment should also be considered. In the studies that reported it, non-completion rates of Alpha-Stim treatment ranged from 0 to 30.4%, the highest figure came from the only UK study (Morriss et al. 2019), with the most common reason being “could not find time to complete treatment”.

There is no evidence on whether the effect of Alpha-Stim is equal across a range of baseline symptom severities.

The EAC recognises that 4 of the 6 included studies also report a reduction in depression scores and that Alpha-Stim may improve depression symptoms on people with generalised anxiety and comorbid depression. A review of out-of-scope studies by the EAC indicates that Alpha-Stim may also be helpful for patients who experience symptoms of anxiety but who do not have a diagnosis of an anxiety disorder. Some experts suggested that Alpha-Stim may be useful for patients with social anxiety disorder or those with anxiety secondary to some long term conditions (which are within the scope of this assessment); the EAC notes there is no published evidence on the use of the device for such patients.

The EAC recognises that social anxiety disorder is within the scope of this assessment. NICE has published guidance on this condition, Social anxiety disorder: recognition, assessment and treatment: Clinical guideline [CG159]. The company submission did not include any reference to the use of Alpha-Stim for the treatment of social anxiety disorder. The experts noted that social anxiety disorder is often poorly diagnosed. Two experts thought Alpha-Stim could be a helpful treatment option for patients with social anxiety, two experts did not think Alpha-Stim was appropriate for these patients, and two experts noted that there was no evidence on the efficacy of Alpha-Stim as a treatment for social anxiety disorder.

8.1 *Integration into the NHS*

One study (Morriss et al. 2019) is set in the UK NHS. This study is a pragmatic study designed to follow standard practice in the IAPT pathway for

patients with generalised anxiety disorder which is highly relevant to the decision problem.

The experts agree that Alpha-Stim is a suitable treatment option for patients with generalised anxiety disorder who have not responded to low intensity psychological interventions. The EAC notes that patients often have to wait to start iCBT treatment, therefore Alpha-Stim could be offered to patients who are on a waiting list. Two experts noted that Alpha-Stim could be helpful in combination with iCBT. Clinical experts also suggest that Alpha-Stim could be offered at an earlier stage in the pathway. The EAC notes the importance of patient choice in this population, therefore the decision to offer Alpha-Stim to patients should be made between the treating clinician and the patient. Some clinical experts also highlighted the importance of patient choice, and that Alpha-Stim offers a drug-free treatment option for patients for whom medication is undesirable, poorly tolerated or has been ineffective, and for patients who are not suited to iCBT.

One expert noted that generalised anxiety disorder can be a long term condition and that courses of Alpha-Stim are likely, in reality, to be one of a number of treatment options employed when patients' anxiety symptoms are particularly severe. Furthermore, the expert noted that once patients have had one or more courses of CBT they rarely gain from further courses. The expert also said that Alpha-Stim can be an option to gain remission from symptoms without the use of drug treatments, some of which can be addictive.

Information from published evidence and the company indicate that the training requirements are not burdensome and that a patient is able to operate the device at home following instructions from a nurse or other healthcare worker.

The EAC conclude that Alpha-Stim may be viewed as an addition to current NICE-recommended treatments for patients who have not responded to step 1 (education and monitoring) and step 2 (low intensity interventions) of the clinical guidelines for generalised anxiety disorder.

Overall the evidence suggests that integration into the NHS pathway would not require significant changes to current practice.

8.2 *Ongoing studies*

The EAC did not identify any ongoing trials following searches of ClinicalTrials.gov or ICTRP. The EAC note that the ongoing study, Royal (2020), in the company submission is likely to be the study with trial number: ISRCTN74799543. The registry entry states that this is a UK-based non-randomised study which "will evaluate the effectiveness of a new treatment pathway designed to optimise the patient experience without increasing the cost burden. It uses new technologies to help patients identify and engage with support, manage symptoms and monitor response". Entry into the study will be offered to attendees at a nurse-led clinic for people who have mental health problems. The registry entry does not state whether an anxiety disorder diagnosis is required for patients to be eligible, although it does state that Alpha-Stim will be a treatment option for those with generalized anxiety. The planned sample size is 100 and the recruitment end date is June 2020.

The company shared preliminary and unpublished results from Dr Royal. These results are presumably from the ongoing study described above but no study title, author, description or methods were provided. The data provided were "initial" and "current" GAD-7 and PHQ-9 scores from 51 participants with patients quotes for some cases. Descriptive statistics and the results of a paired t-test were presented alongside patient-level data with no accompanying narrative or discussion. The EAC have not included these unpublished results because there is not enough information to assess whether the study is relevant to the decision problem or to critique the methodology.

9 Economic evidence

This information in this assessment report relates to the Alpha-Stim AID CES Device.

9.1 *Published economic evidence*

Search strategy and selection

As outlined in section 4.1, the company's search strategy was simplistic, used only free text terms and searched a limited selection of resources. The EAC conducted their own systematic search for both clinical and economic evidence, to include periods from 1st January 1980 to the 12th May 2020. Details of the EAC search are provided in appendix B.

The EAC identified only 1 economic study of Alpha-Stim which met the decision problem outlined in the scope: a cost minimisation analysis by Morriss et al. (2019). This study had also been identified by the company. The company did not identify any other economic evidence.

One additional study, an MSc thesis referenced in the company submission was submitted directly to NICE for consideration and reviewed by the EAC for relevance. The MSc thesis (Hladnik, 2020, unpublished) included in the company submission has been produced by the CEO of a distributor company for Alpha-Stim in Slovenia. The thesis cites the published work by Morriss et al. (2019) and applies a similar decision-tree model approach to the Slovenian health service setting, using Slovenian source costs for iCBT. The thesis finds Alpha-Stim to be cost saving in the range Euro 198 to Euro 382 per patient depending on the selected iCBT comparator and its sequence in the model. The EAC considers the thesis to have low applicability to the UK NHS setting and the thesis is excluded from the EAC list of included studies.

Published economic evidence review

The company's submission includes one published paper based on economic evaluation of Alpha-Stim (Morriss et al. 2019). Briefly, Morriss et al. (2019) is an open-label, non-comparative, observational, cohort study, including consecutive patients with GAD anxiety score >7 who were on the waiting list for iCBT having not reached remission with therapist or full guided self-help.

The study setting was directly applicable as it was conducted in two NHS Improving Access to Psychological Treatment (IAPT) services in the same county in England. The primary outcome was the proportion of patients who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7 as the study notes that the IAPT services are paid for according to the proportion of patients who reach this threshold. Full details of the clinical outcomes including results and limitations are discussed in sections 4 and 5.

The study also included a cost minimisation analysis to determine the cost impact of introducing CES using Alpha-Stim as second line treatment (instead of or prior to iCBT). The EAC critically appraised the publication for methodology using a checklist specifically for health economic studies (CASP 2018) (Appendix H) however as the company confirmed that this publication forms the basis for the de novo cost model submitted to NICE, detailed evaluation and critique of the model and inputs are provided in section 9.2.

The EAC did not identify any additional economic publications for inclusion as direct evidence for the economic submission however it did identify other publications which have been included for background and context. All studies discussed in this section have limited applicability to the decision problem but provide useful background and context to the submitted model and the EAC critique of same. The EAC is aware that there is currently a study ongoing in the primary care setting which potentially includes an economic analysis however there is no data available for review or appraisal at this time (see section 8.2; ISRCTN74799543).

NICE made several research recommendations in CG113. Relevant to the current decision problem is a recognition of the need for further research to answer the question “what is the relative clinical and cost effectiveness of sertraline compared with CBT in people with GAD that has not responded to guided self-help and psychoeducation in a stepped-care model?” The guideline recommends that the cost effectiveness analysis be carried out alongside a randomized trial and that the trial needs to be large enough to determine the presence or absence of clinically important effects and of any differences in costs between the treatment options using a non-inferiority

design (NICE CG113). Crucially the guideline recommends that there should be regular follow-up over a 2 year period to determine whether short-term benefits are maintained.

Morriss et al (2019) is not a randomized trial and the follow-up time is limited to 24 weeks (6 months) and therefore while it reports clinical and cost effectiveness of Alpha-Stim compared with iCBT the results should be interpreted with caution.

Results from the economic evidence

As the results from Morriss et al. (2019) are the same as the results in the de novo cost analysis, they are discussed in detail in section 9.3.

9.2 *Company de novo cost analysis*

Economic model structure

The company model is a simple decision tree with two branches, an iCBT branch and an Alpha-Stim branch (Figure 2). Response rates for the Alpha-Stim branch are based on an empirical study of a series of 161 participants recruited from two different NHS organisations (Morriss et al, 2019). Response rates for iCBT are taken from published literature (Gyani et al, 2013).

In the company base case, all patients entering the iCBT branch receive one course of standard practice iCBT (8 low intensity sessions) with patients who do not respond going on to a second course of standard practice iCBT. In the cohort study by Morriss et al. (2019), all patients were offered Alpha-Stim treatment for up to 12 weeks (6 weeks initially with an option for another 6 weeks) and followed up for an additional 12 weeks. The EAC note that only 22% of patients offered Alpha-Stim agreed to use it. Morriss et al. (2019) comment that this rate of uptake was in response to 'cold calling' patients by telephone to offer Alpha-Stim as therapy, and that uptake may be higher if Alpha-Stim is offered as routine practice. In the economic model, 100% of patients are assumed to use Alpha-Stim and response rates are based on the results reported at 24 weeks. Patients who do not respond to Alpha-Stim are assumed to go on to standard practice iCBT as in the iCBT branch. The EAC considers that the decision tree should reflect the potentially important finding

of the Morriss et al. (2019) study i.e. that a significant proportion of patients offered Alpha-Stim choose not to use it and instead wait for iCBT. The EAC has amended the model structure to reflect this (Figure 3).

Information from three clinical experts relating to current treatment options at this step of the GAD pathway suggests:

- A proportion of patients will choose medication over iCBT
- Patients will generally only have one cycle of iCBT with the number of sessions within that cycle varying
- Non-responders to non-pharmacological interventions will go on to receive medication.

The EAC has therefore presented an alternative decision tree to reflect these factors (Figure 4).

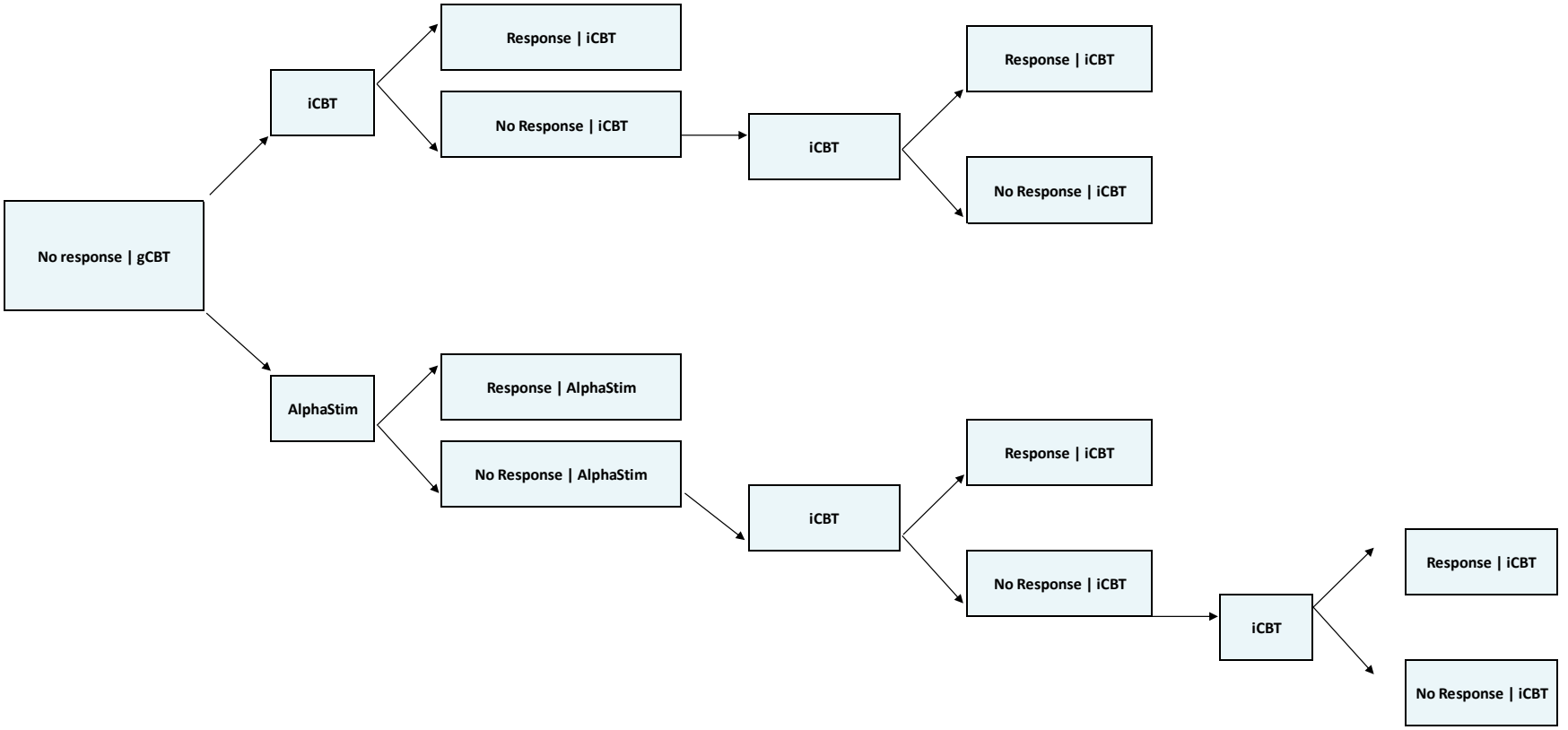
Costs and responses are modelled for 1,000 participants in each arm and the time horizon for the model is 6 months (24 weeks). This represents one cycle of treatment and the expected duration of response to treatment. The EAC note that clinical experts suggest that people with GAD who require high intensity interventions such as iCBT will have cycles of relapse and remission and are likely to require retreatment at various points over their lifetime. The current model does not include any parameters or make any assumptions relating to relapse/remission. Clinical experts suggest that following a successful cycle of treatment, there would be a period of consolidation of up to 12 months whereby the patient would not receive any further intervention. The EAC therefore considers that the current model's 6 month time horizon is appropriate.

Results from the company's economic model are presented as costs for a cohort of 1,000 patients in each arm, presenting the net difference in cost between decision tree branches. The EAC has simply divided these cost by 1,000 to provide a cost per-patient. The model does not present a cost per patient response for each branch or calculate ICERs.

The model is from a UK NHS payer perspective.

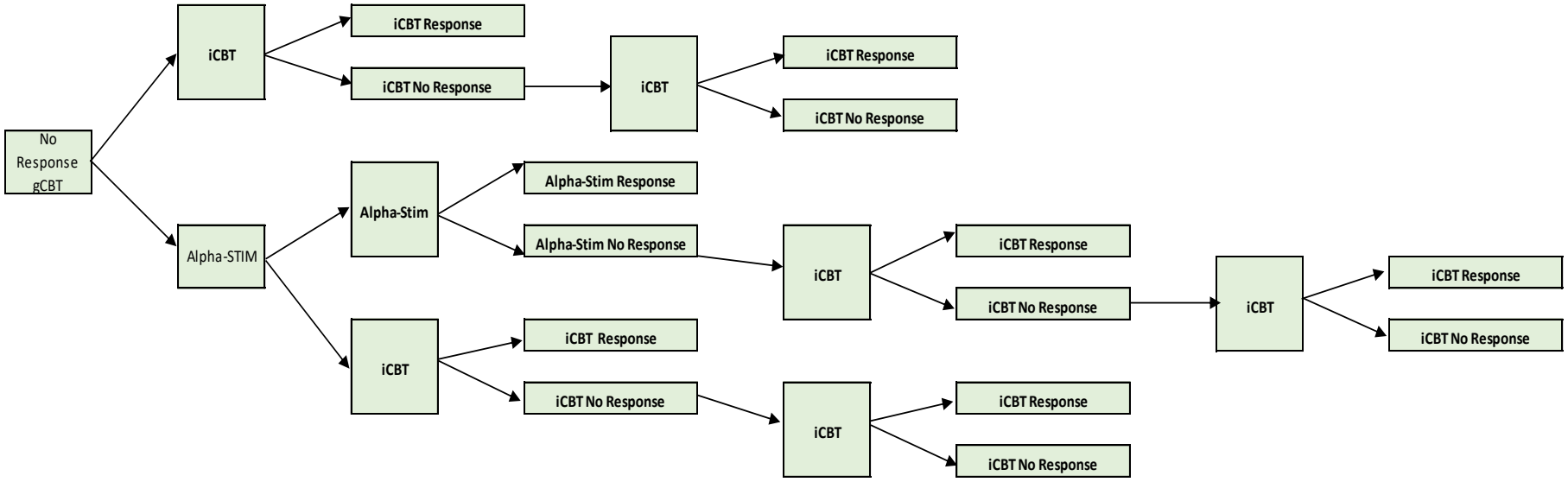
The EAC stress tested the model using extreme input values to ensure functionality and while the model largely functions as expected, the EAC identified one error in the model (Appendix I). The EAC corrected this error but note that it only affects the results if the number of patients using the Alpha-Stim device changes.

The EAC has modified the company model to include a variable rate of uptake of Alpha-Stim (Figure 3). The EAC received information from clinical experts to suggest that medication use should be included and that patients are unlikely to undergo two cycles of iCBT. The EAC has therefore presented an alternative decision tree in which medication is added as a treatment choice at the start of the pathway and as an end point to reflect situations where patients choose to use medication instead of Alpha-Stim or instead of iCBT or as a fallback therapy following no response to Alpha-Stim and/or iCBT. In this EAC base case, only one course of iCBT is provided to patients in both branches (Figure 4).



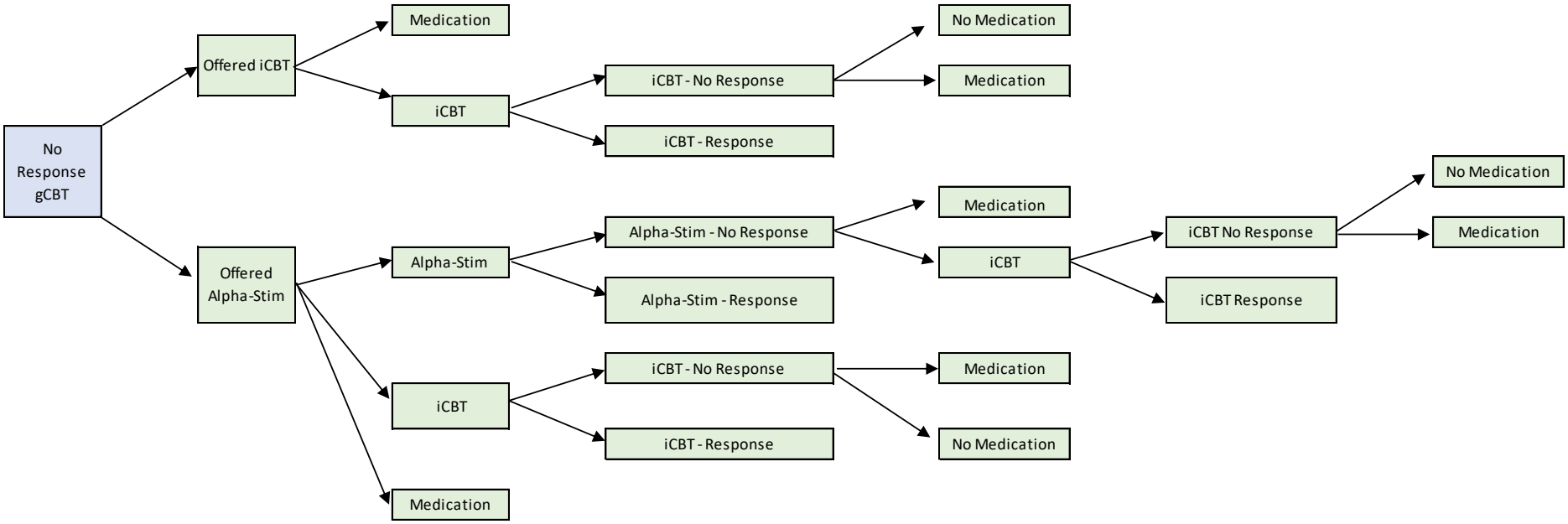
Abbreviations: gCBT, group cognitive behavioural therapy; iCBT, individual cognitive behavioural therapy

Figure 2 - Company Model Decision Tree



Abbreviations: gCBT, group cognitive behavioural therapy; iCBT, individual cognitive behavioural therapy

Figure 3 - EAC Adjusted Company Decision Tree



Abbreviations: gCBT, group cognitive behavioural therapy; iCBT, individual cognitive behavioural therapy

Figure 4 - EAC Decision Tree

Assumptions in the company model

The company described a limited number of assumptions in their submission (Table 7) relating to the response rates with Alpha-Stim and iCBT and to the costs and life span of the Alpha-Stim device. The company model assumes that patients who have failed on initial, low intensity interventions will move onto a waiting list for further high intensity interventions. The NICE pathway for GAD (stepped care model) includes iCBT and drug treatment as options for high intensity treatment. The pathway presented by the company would place Alpha-Stim as an option prior to iCBT or instead of iCBT.

Table 7 - Key assumptions in the company model

Assumption	EAC Comments
Number of patients using Alpha-Stim	
Equal numbers of patients using Alpha-Stim and iCBT	The EAC note that a large number of people who were eligible to use Alpha-Stim, declined to take part in the study (based on a proportion of those approached declining Alpha-Stim of 78%, this would mean that of 732 patients approached, 571 would decline, whereas 161 were recruited (22%)). The EAC note that this may be due to people not wanting to take part in a research study rather than not wanting to use Alpha-Stim, however this information was not collected as part of the study therefore the decision tree should include proportions for both uptake and refusal of Alpha-Stim.
Response Rates	
Probability of Response to iCBT 0.542	The EAC note that as the Alpha-Stim study was a non-comparative study, the only alternative source of response rates for iCBT will be published literature. This should be explored in a deterministic sensitivity analysis. The EAC note that information from three clinical experts suggest this to be a reasonable response rate for iCBT but that the response rate to iCBT may be lower in Alpha-Stim non-responders going on to iCBT.
Probability of Response to Alpha-Stim 0.472	Response rate is the reported response rate at 24 weeks in the empirical study by Morriss (2013). The EAC note that the response rate is likely to be affected by a number of factors including the

	fact that use of medication was not an exclusion criteria for the study but no medication use was recorded. Response rates by Alpha-Stim and also iCBT may be confounded by use of medications. Patients on the waiting list could start iCBT while still using Alpha-Stim. The EAC note that information from three clinical experts suggest that 47.2% is a reasonable response rate for Alpha-Stim.
Probability of response to iCBT remains the same for first and second cycles of iCBT	Some clinical experts suggest that there are no clear 1st and 2nd cycles of iCBT, rather there are variations in the number of sessions a patient receives as part of their iCBT. Alternative clinical expert information (one clinical expert) suggests that a proportion of patients who do not respond to a 1st cycle of iCBT will go on to a 2nd cycle. Based on this, the EAC considers that delivery models for iCBT may differ across service providers or by patient need.
Duration of Alpha-Stim Treatment	
Duration of Alpha-Stim treatment was 6 weeks with an option for a further 6 weeks (Morriss et al). Response was assessed at the end of a 12 week period and again at 24 weeks to assess degree of maintenance. Non-responders to Alpha-Stim would undergo iCBT as per the standard practice model.	The EAC note that the company submission states that Alpha-Stim treatment is recommended for a period of 8 weeks. The EAC has clarified this with the company and they have confirmed that Alpha-Stim is recommended for 12 weeks.
Duration of iCBT treatment	
Initial course of 8 x 60 minute sessions with non-responders undergoing a second course of 8 x 60 minute sessions. This is considered standard care iCBT. Two additional iCBT comparator regimens are included as options (Clark and Wells model and Heimberg model), both are more intensive than standard care iCBT and incur greater cost in the iCBT branch.	The EAC agree that a standard practice iCBT model is a reasonable assumption, however notes that actual delivery models may differ and incorporate elements of all three iCBT models.
Cost of Alpha-Stim per patient	

The life expectancy of a single Alpha-Stim device is expressed as 5 patients treated per device.	The EAC note that the company submission states that the cost of the Alpha-Stim device is £450 (ex VAT) with an expectation that 15 patients would use a single device over its lifetime (5 years). This equates to a cost per patient of £30. An additional £40 per patient is included to cover the estimated cost of additional therapist time, postage and consumables giving a total cost per patient of £70. The EAC note that in the company submission, the cost of Alpha-Stim has been based on 10 week sole use per patient however notes that response rates are calculated from data collected where people had an option to use the device for 12 weeks. The EAC note that in the model, the cost of the Alpha-Stim device is costed at £350 with an expected 5 patients using it over the device lifetime. The EAC is not clear how these figures have been arrived at for the model although note that this gives a cost per patient of £70.
Cost of Alpha-Stim device - £350	
Cost of individual CBT	
60 min iCBT session - £110.96	The costs for a 60 min and 90 min session of iCBT have been taken from published literature and inflated to current costs. There is no indication that these costs have been validated by a clinical expert. Clinical experts have indicated to the EAC that these seem like appropriate costs per session.
90 min iCBT session - £199.17	

Economic Model Parameters

The EAC review suggests that while Alpha-Stim may be an alternative to iCBT there are a number of additional elements that have not been included in the company economic assessment and that are likely to impact any potential cost savings. In addition, clinical expert information has indicated a number of possible treatment scenarios for patients who have not responded to low intensity interventions. The EAC has adjusted the company base case to reflect the uptake of Alpha-Stim and presented an alternative base case to that submitted by the company. The EAC has also presented an alternative

base case which includes medication use and which the EAC considers better reflects the clinical pathway. To explore comments made by clinical experts that not all non-responders to first cycle of iCBT will have a second cycle, an additional scenario is a presented which reduces the proportion of patients having a second cycle of iCBT.

Model	**EAC Comment**
Company Base Case	Model submitted by the company as published in Morris et al (2019). No adjustment for low uptake of Alpha-Stim
Adjusted Company Base Case	Company model, adjusted by EAC to include low uptake of Alpha-Stim and reflect patients who decline Alpha-Stim and incur the cost of iCBT in the Alpha-Stim arm Minor alterations to calculations and updates to costs.
EAC Base Case	Decision tree re-worked to include • low uptake of Alpha-Stim as above • choice of medication as a treatment option (no response rates to medication included) • No 2nd cycle of iCBT (instead the number of sessions of iCBT per cycle is varied in the sensitivity analysis)
Scenario 1	Uses EAC base case

	• All patients who do not choose medication will be treated using Alpha-Stim as first treatment option.
Scenario 2	Uses the adjusted company model • Lower response rate in second cycle of iCBT (based on clinical expert input)
Scenario 3	Uses EAC base case • Adds Alpha-stim as an option for patients who initially choose iCBT but do not respond (response to a request from the company during fact check) • Option is added to the Alpha-Stim branch only

Adjusted Company Base Case: A high proportion of patients will not take up the offer of Alpha-Stim

The key element identified by the EAC is related to the uptake of Alpha-Stim by patients. The only published UK evidence suggests that only 22% of patients who were offered Alpha-Stim, agreed to use it (Morriss et al, 2019) and one clinical expert highlighted the low uptake as an area for investigation. The EAC considers that this would have an impact on the potential cost savings as a large proportion of patients will go straight to iCBT thus incurring the higher cost of iCBT. The EAC therefore presents a scenario which accounts for the proportion of patients who refused Alpha-Stim while on the waiting list for iCBT. The EAC acknowledges that there are valid reasons why the uptake of Alpha-Stim in the clinical study was so low including that the patients were cold called by the company to invite them to take part. The EAC

conducted threshold analysis to assess the impact of different rates of uptake. Assumptions used in the adjusted company base case are described in Appendix K.

EAC Base Case: A proportion of patients will choose pharmacological interventions (medication) over non-pharmacological interventions (Alpha-Stim or iCBT), will start medication, not have a second cycle of iCBT and a proportion of patients who do not respond to non-pharmacological treatments.

One other key element for consideration is the use of medication in both arms. The company base case does not include medication use at any point. Although the NICE GAD pathway suggests that iCBT and drug treatments are equal choices, clinical experts suggest that the true clinical scenario is more likely to be some patients choosing to have medication rather than continue down a non-pharmacological route or having a combination of both treatment types. Published literature (Morriss et al 2019) suggests that the same is true for Alpha-Stim. Three clinical experts suggest that selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed drugs. NICE guidance recommends that the SSRI sertraline be considered as the first drug option as it is the most cost effective. In addition, the EAC consider it unlikely that non-responders to non-pharmacological interventions would receive no further treatment. The EAC has therefore presented an alternative base case in which a proportion of patients choose medication (sertraline) over iCBT or Alpha-Stim. In this model, all non-responders to non-pharmacological interventions have the option to go on to have medication. The EAC model includes medication as a cost-incurring end point; the EAC model does not consider a response rate to medication.

One clinical expert suggests that it is unlikely that there would be a second cycle of iCBT, instead the number of sessions of iCBT a patient receives as part of their treatment can vary widely. NICE guidelines suggest that the number of sessions of iCBT should range from 12-15 weekly sessions whereas information on NHS choices states that patients will have between 5 and 20 face to face sessions. The EAC has therefore removed the second

iCBT cycle but has varied the number of session of iCBT to reflect the possible range and cost.

Assumptions used in the EAC base case are described in Appendix L.

Scenario 1: All patients who do not choose medication, choose Alpha-Stim before iCBT. Alpha-Stim non-responders move to iCBT or medication.

Scenario 1 is based on the EAC base case and was added following discussion with an IAPT expert.

The EAC rationale for including the 22% uptake was in part due to one clinical expert expressing concern about the low uptake. In addition, based on the pathway presented by the company (offer Alpha-Stim while on waiting list for iCBT with non-responders going on to iCBT), the EAC assumption is that patients who do not agree to take Alpha-Stim while on the waiting list for iCBT will then incur the cost of the more expensive treatment option (iCBT) whereas had they agreed to use Alpha-Stim, patients responding to Alpha-Stim would not incur the cost of iCBT. The EAC acknowledge however that this may not be appropriate to account for low uptake in this manner and has therefore also presented results of the EAC base case with all patients who do not choose medication, choosing Alpha-Stim before iCBT.

Scenario 2: A proportion of patients who do not respond to the 1st cycle of iCBT do not go on to a 2nd cycle and response rates to iCBT reduce to 50% for Alpha-Stim non-responders and 1st iCBT non-responders

Scenario 2 is based on the adjusted company base case.

There was some suggestion from two clinical experts that patients who do not respond to a first cycle of iCBT will not go to a second cycle and that if they do, the response rate to a second cycle is likely lower than for a first cycle. In addition, clinical experts suggest that patients who do not respond to Alpha-Stim are also likely to have slightly reduced response rates to iCBT. The EAC has therefore modelled a scenario in which 50% of non-responders go on to

have a second cycle of iCBT and the response rate is reduced from 54.2% to 50%.

Scenario 3: Patients in the Alpha-Stim arm who choose iCBT as first treatment and do not respond, may choose to try Alpha-Stim before medication.

Scenario 3 is based on the EAC base case and was added following fact check.

The EAC base case does not include a situation where patients who choose iCBT as their first treatment and do not respond, can choose to try Alpha-Stim before moving to medication. Information from the company suggest that this may be a possible option. The EAC accept that there may be situations where patients who initially refused Alpha-Stim in favor of iCBT and did not respond to iCBT, might be willing to reconsider Alpha-Stim before medication. The EAC therefore modelled a scenario where of the patients who do not respond to iCBT, a proportion will choose to move straight to medication (15%) and of the remaining patients, 22% will choose Alpha-Stim before moving medication. Full details of this scenario, including an adjusted decision tree are available in Appendix M.

Clinical parameters and variables

The only parameters included in the company model are response rates for Alpha-Stim and iCBT (Table 8) and costs for Alpha-Stim and iCBT (Table 9).

The probability of response to iCBT has been derived from published literature (Gyani et al, 2013) and a range applied for sensitivity analysis. The company submission does not provide details of how the values for the range were calculated but they appear to be ±10% of the point estimate.

The probability of response to Alpha-Stim has been derived from company data (Morriss et al, 2019) and again an upper and lower value included for sensitivity analysis. No details on how the range was calculated are provided in the company submission.

Information from three clinical experts suggests that the response rates for both Alpha-Stim and iCBT used in the company model are valid, although one clinical expert does suggest a slightly lower response to iCBT in patients who do not respond to Alpha-Stim.

The company submission chose a 'Standard Practice' model of iCBT delivery for their base case. This comprises 8 low intensity sessions (60 mins) of iCBT per treatment with non-responders undergoing a second course of iCBT (8 x 60 min sessions). The model assumes a maximum of 2 cycles of iCBT treatment.

Table 8 - Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Probability of response to iCBT	0.542 (0.49-0.59)	Published literature (Gyani et al, 2013)	0.542 (0.4336 to 0.650)	The range is used in the PSA but the EAC note that no explanation or justification is given for the range used. It appears to be ±10% of 0.542. Clinical expert advice (3 experts) suggests that these are reasonable response rates. The EAC has not changed the probability of response but has widened the range in the deterministic sensitivity analysis to ±20%.
Probability of response to Alpha-Stim	0.472 (0.38-0.48)	Company data	0.472 (0.3776 to 0.5664)	The range is used in the PSA but the EAC note that no explanation or justification is given for the range used. The EAC notes that although the probability of response is published in Morriss et al (2019), there is no mention of a range of responses. Clinical expert advice (3 experts) suggests that these are reasonable response rates. The EAC has not changed the probability of response but has widened the

Variable	Company value	Source	EAC value	EAC comment
				range in the deterministic sensitivity analysis to ±20%.
Choice of iCBT delivery model	Standard Practice (8 low intensity sessions)	Clinical Experts	No Change	The company base case model uses a 'Standard Practice' model of iCBT. Two alternative models (Clark and Wells and Heimberg) are included as options for comparison. The company submission states that the number of sessions in the Standard Practice model was validated by experts as part of the cohort study. The EAC agrees with the choice of standard practice as a reasonable assumption but note that clinical experts suggest that the true number of sessions a patient undergoes may vary widely. The EAC has therefore kept to a standard practice model but has explored the impact of changing the number of iCBT sessions in the alternative base case. The EAC note that in table 3 of the company submission, standard practice includes only 8 low intensity (60 min) sessions and 8 high intensity (90 min) sessions. The company have confirmed that this is an error and standard practice comprises 8 low intensity sessions per cycle.
Medication Use (Sertraline)	Not Included		15% of patients who do not respond to gCBT will	Information from one clinical expert suggests that between 10 and 15% of patients will chose medication over non-

Variable	Company value	Source	EAC value	EAC comment
			chose medication over non-pharma-cological alternatives	pharmacological treatment options. The EAC has also included an assumption that non-responders to non-pharmacological interventions are likely to be prescribed or offered medication. The EAC has explored the impact of including the cost of medication (based on the cost of 6 months' use of sertraline 50mg/day plus the cost of 3 x General Practitioner consultations) in the alternative base case model.

Resource identification, measurement and valuation

Costs are included as 'bundle' costs, that is a single cost per patient for Alpha-stim which includes parameters such as therapist time and consumables and a cost per session for iCBT which includes staff costs.

The company submission does not include any costs for medications prescribed during the course of treatment with Alpha-Stim or iCBT.

Table 9 - Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	EAC value	Source	EAC Comment
Cost of Alpha-Stim	£70 per patient	£70 per patient	Company Submission	The EAC note there are some inconsistencies with the way the cost for Alpha-Stim has been calculated (see Table 7). The cost of Alpha-Stim has been calculated based on a cost per unit divided by the number of patients expected to use the device. Additional costs for factors such as

Parameter	Company value	EAC value	Source	EAC Comment
				postage, therapist time and consumables are included. The EAC agree this is an appropriate way to calculate a cost per patient.
Cost of iCBT (Standard Practice)	£887.86 per cycle	£899.92 per cycle	Published Literature	The total cost of iCBT is based on a cost of £98.59 per 60 min session (Radhakrishnan et al. 2013) uplifted to £110.96 with 8 sessions per cycle in the standard practice model. The EAC used the same cost (£98.59) uplifted to 2017/2018 costs to give a cost per session of (£112.49).
Cost of iCBT (Clark and Wells)	£2,788.43 per cycle	£2,827.02 per cycle	Published Literature	The total cost of iCBT is based on a cost of £98.59 per 60 min session and £176.97 per 90 min session (Radhakrishnan et al. 2013) uplifted to £110.96 and £201.93 respectively. Clark and Wells Model: 14 x 90 min sessions.
Cost of iCBT (Heimberg)	£1,863.57 per cycle	£1,889.28 per cycle	Published Literature	The total cost of iCBT is based on a cost of £98.59 per 60 min session and £176.97 per 90 min session (Radhakrishnan et al. 2013) uplifted to £110.96 and £201.93 respectively. Heimberg Model: 15 x 60 min sessions plus 1 x 90 min session.
Cost of medication	Not included	£127.24	British National Formulary (2020) PSSRU (Curtis et al. 2019)	Cost of 6 months sertraline of £8.30 (based on £0.05 per tablet for 183 days) cost of 3 GP appointments over a 6 month period of £118.94 (based on cost of £4.30 per minute of GP time * 3 appointments of 9.22mins (mean duration of visit).

Parameter	Company value	EAC value	Source	EAC Comment
				This cost applies to the EAC alternative base case only.

Sensitivity analysis

The company submission included a probabilistic sensitivity analysis (PSA) run for 5,000 iterations to quantify the level of confidence around the model inputs. A beta distribution was used for the probability of response and gamma distribution for the costs of the iCBT. The EAC considers the choice of distributions to be appropriate.

The company submission also included a one way deterministic threshold analysis to identify the cost at which Alpha-Stim becomes cost-incurring.

The EAC carried out a deterministic sensitivity analysis for each scenario to calculate a best and worst case result. Threshold analysis was carried out to assess the impact of varying the rate of uptake of Alpha-Stim as well as the cost of Alpha-Stim.

9.3 *Results from the economic modelling*

Base case results

The base case as presented in the company economic submission is a simple cost difference between the cost per patient for Alpha-Stim (£70) and the cost per patient for iCBT (£887.68) which suggests that Alpha-Stim is cost-saving compared with iCBT (-£817.68).

The EAC has concerns with this as the base case. The cost the company have presented as their base case is not an incremental cost per-patient for Alpha-Stim. The EAC considers it is just a per-patient cost to provide the technology based on the cost of a device and the number of patients expected to use it over its life-time. The incremental cost per-patient for Alpha-Stim needs to include the cost of subsequent iCBT treatments for patients who do not respond to Alpha-Stim treatment.

Similarly, the cost for iCBT is stated to be a cost per patient in the company submission however the EAC consider this to be a cost per cycle of iCBT

(£110.96*8 sessions). The incremental cost per-patient needs to account for patients who do not achieve remission on a first cycle of iCBT and go on to a second cycle.

The EAC therefore considers the company base case to be the results presented in the economic model (Table 10). The EAC notes that the high and low values for the base case are derived from the probabilistic sensitivity analysis and therefore change slightly every time the PSA is run. The adjusted base case and EAC base case include a deterministic sensitivity analysis to calculate the high and low values.

Results of the company base case, the adjusted base case and the EAC base case are presented in table 10 alongside 3 alternative scenarios.

Table 10 - Summary of base case results

Company Base Case Results				
Alpha-Stim (per patient)	**iCBT (per patient)**	**Cost saving per patient**	**High Value**	**Low Value**
£753.35	£1,294.23	-£540.88	-£648.60	-£314.59
Adjusted Base Case Results (22% of patients use Alpha-Stim)				
Alpha-Stim (per patient)	**iCBT (per course of treatment)**	**Cost saving per patient**	**High Value**	**Low Value**
£1,191.24	£1,312.08	-£120.85	-£396.92	-£31.12
EAC Base Case (15% of patients choose medication, no 2nd iCBT, all non-responders can choose to go on to medication)				
Alpha-Stim (per patient)	**iCBT (per course of treatment)**	**Cost saving per patient**	**High Value**	**Low Value**
£728.00	£808.79	-£80.79	-£570.80	-£0.28
Scenario 1 Results (all patients not choosing medication will receive Alpha-Stim)				
Alpha-Stim (per patient)	**iCBT (per course of treatment)**	**Cost saving per patient**	**High Value**	**Low Value**
£441.57	£808.79	-£367.22	-£1,238.03	-£2.53
Scenario 2 Results (reduced proportion of patients move onto 2nd iCBT, reduced response to subsequent treatments)				
Alpha-Stim (per patient)	**iCBT (per course of treatment)**	**Cost saving per patient**	**High Value**	**Low Value**
£1,008.75	£1,106.00	-£97.25	-£375.56	-£50.47

Scenario 3 Results (proportion of patients who do not respond to iCBT as first treatment option will choose to try Alpha-Stim before medication)				
Alpha-Stim (per patient)	**iCBT (per course of treatment)**	**Cost saving per patient**	**High Value**	**Low Value**
£720.36	£808.79	-£88.43	-£626.18	-£0.88

In all scenarios presented by the company and the EAC, Alpha-Stim is cost-saving compared with iCBT.

The company base case suggests that the saving is -£540.88 per patient compared to iCBT. In the adjusted base case however, where only 22% of patients agree to use Alpha-Stim, the cost saving is reduced to -£120.85 (-£31.12 to -£396.92) per patient compared to iCBT.

In the EAC base case in which a proportion of patients receive medication, the cost saving is further reduced to -£80.79 per patient compared to iCBT (-£0.28 to -£570.80) when applying the 22% uptake rate. If all patients get Alpha-Stim (scenario 1), the cost savings are -£367.22 (-£1,238.03 to -£2.53).

In scenario 2 where a proportion of patients receive a second cycle of iCBT but the response rate is slightly lower, the cost saving is -£97.25 (-£50.47 to -£375.56).

In scenario 3 where a proportion of patients who did not respond to iCBT as first treatment choose Alpha-Stim before medication, the cost saving is -£88.43 (-£0.88 to -£626.18). See appendix M for full details and sensitivity analysis.

Sensitivity analysis results

Results of the company probabilistic sensitivity analysis suggest that Alpha-Stim is cost saving in 99.9% of iterations. The EAC performed deterministic sensitivity analysis the results of which suggest that the uptake of Alpha-Stim is the key driver in the adjusted base case (Figure 5).

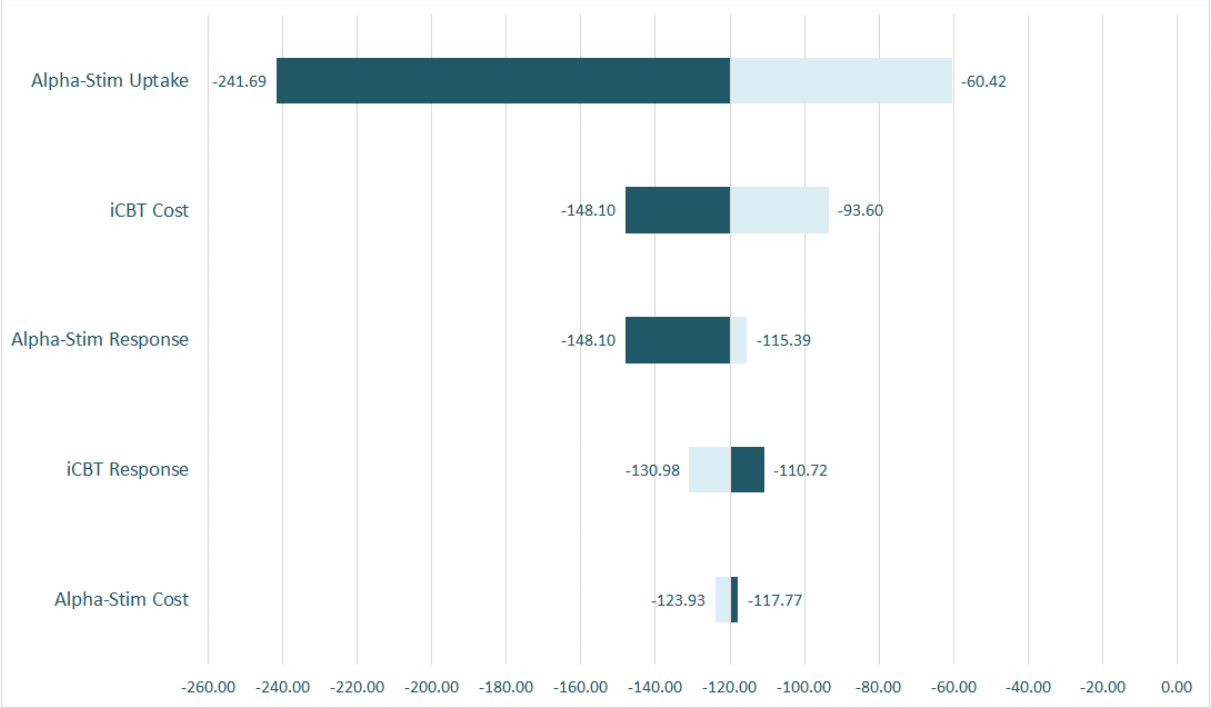


Figure 5 - Tornado Diagram for EAC Adjusted Base Case

In the EAC base case, cost of iCBT which is reflective of the number of sessions of iCBT (range 2 to 20 sessions) and uptake of Alpha-Stim were the two key drivers impacting the results (Figure 6).

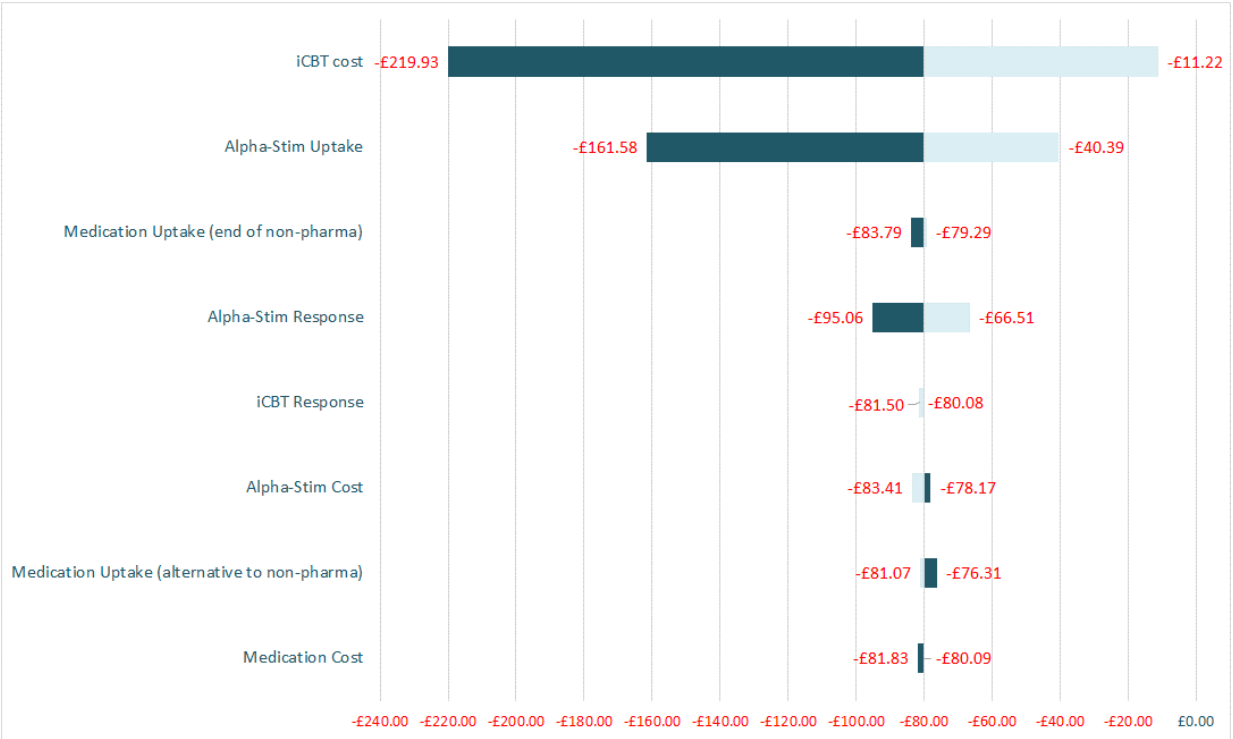


Figure 6 - Tornado Diagram for EAC Alternative Base Case

Results of a one way deterministic threshold analysis performed by the company suggest that at a cost of £610.88, Alpha-Stim becomes cost incurring. In the EAC base case, the threshold cost at which Alpha-Stim becomes cost-incurring is approximately £503.

The EAC notes that medication use is likely to be more complex than is reflected in the alternative base case and there are a number of possible factors which are not addressed by the alternative base case approach due to a lack of data. The EAC recognises that the proportion of patients who choose to take medication may not be equal across both arms. The EAC undertook an exploratory analysis in which the proportion of patients taking medication as an alternative to non-pharmacological treatments is varied differentially (range 10% to 70%) across the two arms. This changes the numbers of patients diverted to medication, and in turn the number of patients routed to Alpha-Stim and iCBT. The results suggest that when medication use is high in the iCBT arm and low in the Alpha-Stim Arm, Alpha-Stim becomes cost-incurring due to the higher proportion of patients in the iCBT branch selecting a less expensive treatment option (medication). If medication use is high in the Alpha-Stim arm and low in the iCBT arm, Alpha-Stim remains cost saving (Figure 7).

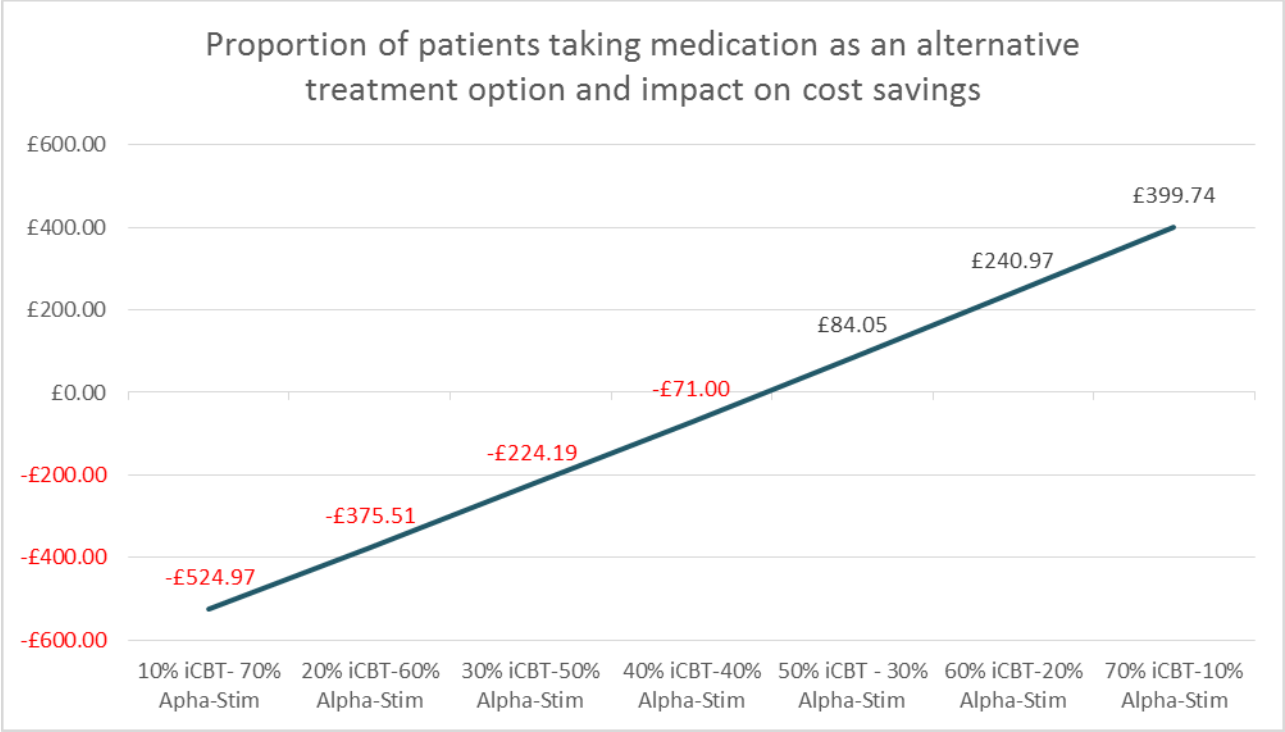


Figure 7 – Effect of different proportions of patients in each arm using medication as an alternative treatment option

9.4 *The EAC's interpretation of the economic evidence*

The EAC agrees that the model submitted by the company is a plausible representation of the clinical pathway if Alpha-Stim were to be offered to patients prior to iCBT with non-responders retaining the option to move to iCBT. In this setting, patients who respond to Alpha-Stim would not require further iCBT thus reducing the cost per patient of treatment while potentially freeing up resource to deliver iCBT to patients who do need it. In the company submission, the assumption appears to be that 100% of patients offered Alpha-Stim will use it and given the response rate (47.2%) and the lower cost of treatment, the EAC agrees that a reduction in iCBT appointments and cost is realistic. The EAC made one key change to company submission to represent the fact that only 22% of patients agreed to use Alpha-Stim (Morriss et al, 2019). The results of this change are that while Alpha-Stim is still cost-saving per patient, the cost-saving per patient is reduced. This is due a greater number of patients going straight on to iCBT and incurring iCBT costs

in the Alpha-Stim arm. Tornado diagrams indicate that the biggest driver for the cost-saving is the rate of Alpha-Stim uptake.

The EAC notes that the clinical scenario is more likely to be that patients who do not respond at step 2 of the IAPT pathway (low intensity, non-pharmacological interventions such as gCBT) are likely to have a choice as to whether they continue with a non-pharmacological approach to treatment (iCBT or Alpha-Stim) or to move to a pharmacological approach (Sertraline or other medication) or to a combination of non-pharmacological and pharmacological treatments. In addition, the EAC notes that it is likely that all treatment options will be explored before a decision to move to step 4 of the treatment pathway. This means that non-responders to non-pharmacological interventions are likely to receive medication such as sertraline. In the alternative base case, the EAC has also removed the option for a 2nd line of iCBT as clinical experts suggest that it is more likely that the number of sessions a patient receives will likely be determine by need and in discussion with the patient and can range between 2 and 20 sessions. The EAC investigated the impact of this by altering the cost of iCBT in the sensitivity analysis to reflect the high and low number of sessions. Results of this alternative base case remain cost saving (-£80.79) per patient compared with iCBT. Tornado diagrams again indicate that the uptake of Alpha-Stim is one of the key drivers although not the main driver. As expected, the cost of iCBT has the biggest impact on the results in this scenario. In the EAC alternative base case, increasing the uptake of Alpha-Stim to 44%, increases the cost saving to £161.58 per patient and increasing uptake to 100% increases the cost saving to -£367.22 (all other variables in the model kept to base case values) indicating that the greater the number of patients who choose to use Alpha-Stim, the greater the cost-savings can be achieved.

The key benefits claimed by the company is that introduction of Alpha-Stim will reduce the need for individual CBT and reduce the cost for treatment of anxiety compared with the current pathway, presenting significant cost-savings.

The EAC considers that the introduction of Alpha-Stim has the potential to be cost saving even when considering the addition of medication use to the model and even at a low rate of uptake of Alpha-Stim. This is due to fewer patients in the Alpha-Stim arm having iCBT. None of the scenarios presented resulted in Alpha-Stim becoming cost-incurring although the low value in the EAC base case was -£0.88 cost saving which suggests that, assuming all other parameters are included appropriately, there are scenarios where the introduction of Alpha-Stim may be cost-neutral. The EAC notes however that advice from an IAPT expert indicates that the combined response rates for Alpha-Stim followed by iCBT may be unrealistically high and therefore merit further careful discussion.

In 2018/2019 a total of 228,525 patients received both low and high intensity therapies and 134,147 patients received only high intensity treatments through the IAPT (IAPT 2019). Completion rates for therapies were 39.2% and 23% respectively suggesting a high proportion of patients do not complete their course of treatment. The low rate of Alpha-Stim uptake may therefore be indicative of something other than a reluctance to use the device, however it should be noted that these figures relate to all disorders and are not restricted to GAD. Alpha-Stim is currently placed as an option for patients who are on the waiting list for high intensity therapies. According to IAPT figures, the majority of patients wait ≤28 days for treatment on the pathway and as Alpha-Stim treatment is six weeks with an option for an additional six weeks, patients may refuse Alpha-Stim treatment or discontinue treatment before completion as they are offered high intensity treatments.

The EAC considers that the claimed benefits are therefore plausible but the extent of the benefit is dependent on the number of patients using Alpha-Stim and avoiding iCBT as well as on the cost of delivering iCBT. The EAC considers that there are complexities of the treatment pathway which may not be captured in the current analysis such as treatment completion rates for current therapies, reasons for non-completion, use of medication and the position of Alpha-Stim in the pathway.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The evidence on Alpha-Stim as a treatment for anxiety disorders is comprised of a small number of studies including two published randomised trials, one unpublished RCT, and three observational studies, with UK NHS specific evidence limited to one recent, non-comparative, prospective observational study. The included studies are small (the largest study has a sample of 197 participants) and all are at some risk of bias. Five of the 6 studies include participants with generalised anxiety disorder.

Adverse events from Alpha-Stim use are rare and self-limiting and the EAC concludes that use of Alpha-Stim does not raise any safety concerns.

Overall the published evidence suggests that patients with generalised anxiety disorder may benefit from using Alpha-Stim. Statistically significant improvements in anxiety symptom scores (measured using validated questionnaires in all but one study) were observed in participants treated with Alpha-Stim. The sustainability of this benefit is unclear as only one study followed up patients for more than 6 weeks. This study showed that improvements in anxiety symptoms were maintained at 24 weeks.

In one published RCT, the Alpha-Stim group reported a significantly greater reduction in anxiety symptoms scores from baseline to week 5 than the sham device group, and 83% of the Alpha-Stim group achieved recovery (comparator recovery rate was not reported). In the other published RCT, participants treated with Alpha-Stim and paroxetine for 6 weeks showed improved anxiety scores compared to those treated with paroxetine alone; in this study 76.7% of the Alpha-Stim plus paroxetine group achieved recovery compared to 53.3% in the paroxetine alone group. The generalisability of these findings to an NHS setting where participants have not responded to low-intensity interventions is limited.

Only one study is set in the UK NHS (non-comparative, observational), this is highly relevant to the decision problem. This reported that 44.7% of

participants achieved remission at 12 weeks. The absence of a control group means that improvements in anxiety scores cannot be attributed to Alpha-Stim with certainty. A large proportion of eligible potential participants in this study refused to take part, and there was a high level of drop-out after study treatment which may indicate poor interest and tolerance to the device treatment regime (although 2 of the 49 patients who withdrew from treatment did so because they felt better, and 30 gave no reason). In this study 49.7% of participants needed iCBT after treatment with Alpha-Stim.

The small number of comparative studies and heterogeneity in their design means that the EAC did not carry out an independent meta-analysis.

Clinical experts agree that Alpha-Stim is a suitable treatment option for patients with generalised anxiety disorder who have not responded to low intensity psychological interventions. The EAC notes that patients often have to wait to start iCBT treatment, therefore Alpha-Stim could be offered to patients who are on a waiting list. The EAC also notes the importance of patient choice in this population, therefore the decision to offer Alpha-Stim to patients should be made between the treating clinician and the patient.

There is no evidence on whether Alpha-Stim reduces the use of medication for anxiety and the available evidence does not support its use as a replacement for pharmaceutical therapy.

There is no evidence on whether the effect of Alpha-Stim is equal across a range of baseline symptom severities.

10.2 *Conclusions from the economic evidence*

The company claims that the introduction of Alpha-Stim can achieve significant cost savings through a reduction in the number of patients needing iCBT however the results presented by the company were based on assumption that 100% of patients offered Alpha-Stim would use it and included no medication costs. The EAC base case included only 22% of patients using Alpha-Stim as well as including costs for a proportion of patients using medication.

The company base case and all scenarios investigated by the EAC indicate that Alpha-Stim results in a cost-saving when added as a treatment option to Step 3 of the IAPT pathway although the degree of cost saving varies from £540.88 per patient (company model) to £80.79 per patient (EAC base case).

In the EAC base case, medication use is included as an alternative treatment choice to non-pharmacological treatments and as an option following non-response to non-pharmacological treatments. Medication in combination with non-pharmacological treatments is not included. The EAC modelled only the cost of one medication (Sertraline) as this is the recommended first choice of medication in the NICE guidelines (CG113). In reality, there will be patients who use medication in addition to non-pharmacological treatments and the choice and cost of medications will vary which may impact the results. The EAC also explored the impact of varying medication use in Alpha-Stim arm compared with the iCBT arm. The results suggest that high medication use in the iCBT arm and low medication use in the Alpha-Stim arm potentially results in Alpha-Stim becoming cost-incurring due to the fact that medication is much less expensive that iCBT. The EAC considers it important to try consider the impact of the complex nature of medication use in the pathway and the potential role for Alpha-Stim.

The EAC considers that the key factor driving the extent of the cost-saving is likely to be the proportion of patients who choose to use Alpha-Stim with higher numbers using the device leading to greater cost savings. In addition, the number of iCBT sessions required will have a significant impact on potential cost-savings as the fewer sessions of iCBT required the lower the cost of iCBT.

Overall, the EAC considers that the evidence suggests that the introduction of Alpha-Stim as a treatment option following failure to respond to low intensity non-pharmacological options is likely to be cost-saving compared with iCBT.

11 Summary of the combined clinical and economic sections

The clinical evidence on Alpha-Stim as a treatment for anxiety disorders is based on a small number of studies which are at risk of bias. Overall the published evidence suggests that patients with generalised anxiety disorder may benefit from using Alpha-Stim. Statistically significant improvements in anxiety symptoms were observed in participants treated with Alpha-Stim in the short term (6 weeks). Long term benefits were only reported in one study which showed improvements in anxiety were sustained for 24 weeks. Clinical experts agree that Alpha-Stim is a suitable treatment option for patients with generalised anxiety disorder who have not responded to low intensity psychological interventions. The company base case and three scenarios investigated by the EAC indicate that Alpha-Stim is a cost-saving treatment option compared to iCBT in the NHS for patients who do not respond to low intensity treatment interventions. The number of patients who use Alpha-Stim and the number of iCBT sessions in the comparator arm will have the largest impact on the potential cost-savings from Alpha-Stim.

Benefit claimed by company	EAC opinion on whether claimed benefit is supported by evidence
Patient benefits	
Reduction in anxiety symptoms	Yes (based weak evidence)
Reduced reliance on medications	No
System benefits	
Reduced need for Cognitive-Behavioral Therapy (CBT)	Yes (extent of cost saving may be lower than presented by company, possibility of cost neutral)
Improved treatment in subgroups where additional medication is contraindicated	No (addition of Alpha-Stim provides alternative treatment, no evidence that it would improve treatment in subgroups)
Cost benefits	

Reduced cost for treatment of anxiety compared to current pathway.	Yes (based on assumptions around uptake and costs of other treatments) Careful consideration of response rates used in the model needed
Sustainability benefits	
Patients can re-use Alpha-Stim devices in their homes.	Unclear (patients use device at home but return it to NHS provider after 6-12 weeks of treatment)

12 Implications for research

The EAC recognises the need for high quality UK-based studies directly comparing the relative effectiveness of Alpha-Stim and other treatments (e.g. non-pharmacological and/or pharmacological interventions) in people with GAD that have not responded to low-intensity treatments in the stepped-care model. The most appropriate approach to addressing this evidence gap is through a pragmatic randomised controlled trial carried out in the UK NHS setting where Alpha-Stim would be used (likely in the IAPT service, but GP primary care should also be considered). The study should have a 2 year follow-up to evaluate the sustainability of any symptom improvements (the research recommendations from NICE CG113 on the management of generalised anxiety disorder states that follow-up of a study on sertraline versus CBT should be 2 years to ascertain whether short-term benefits are maintained). The study should collect data on previous and current pharmacological and non-pharmacological treatments for anxiety throughout the pathway to investigate whether Alpha-Stim leads to a reduction in other treatments. Alongside validated condition specific patient-reported outcome measures, the study should gather utility data using a tool such as EQ-5D to facilitate a more detailed cost-effectiveness analysis of Alpha-Stim.

The EAC recognises that social anxiety disorder is included in the decision problem for this assessment. No evidence was identified on the use of Alpha-Stim to treat this condition. Advice from experts suggested that the treatment

pathway for social anxiety disorder is less well established. Should NICE wish to recommend further research on patients with this condition, the EAC would recommend a detailed feasibility and pilot study to investigate the patient pathway, current standard practice, outcome measures, and whether Alpha-Stim is likely to be suitable.

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14 Appendices

Appendix A: Details from NICE Clinical Guideline (CG113)

Stepped care pathway for the management of generalised anxiety disorder and panic disorder in adults.

Focus of the intervention	Nature of the intervention
STEP 4: Complex treatment-refractory GAD and very marked functional impairment, such as self-neglect or a high risk of self-harm	Highly specialist treatment, such as complex drug and/or psychological treatment regimens; input from multi-agency teams, crisis services, day hospitals or inpatient care
STEP 3: GAD with an inadequate response to step 2 interventions or marked functional impairment	Choice of a high-intensity psychological intervention (CBT/applied relaxation) or a drug treatment
STEP 2: Diagnosed GAD that has not improved after education and active monitoring in primary care	Low-intensity psychological interventions: individual non-facilitated self-help*, individual guided self-help and psychoeducational groups
STEP 1: All known and suspected presentations of GAD	Identification and assessment; education about GAD and treatment options; active monitoring
* A self-administered intervention intended to treat GAD involving written or electronic self-help materials (usually a book or workbook). It is similar to individual guided self-help but usually with minimal therapist contact, for example an occasional short telephone call of no more than 5 minutes.	

Step 3

The NICE pathway on GAD states that if a person with GAD chooses a high-intensity psychological intervention, offer either CBT or applied relaxation. Practitioners providing high-intensity psychological interventions for GAD should:

- have regular supervision to monitor fidelity to the treatment model, using audio or video recording of treatment sessions if possible and if the person consents
- use routine outcome measures and ensure that the person with GAD is involved in reviewing the efficacy of the treatment.

CBT should:

- be based on the treatment manuals used in the clinical trials of CBT for GAD
- be delivered by trained and competent practitioners

- usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour.

Applied relaxation should:

- be based on the treatment manuals used in the clinical trials of applied relaxation for GAD
- be delivered by trained and competent practitioners
- usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour.

In relation to drug treatment, NICE states, if a person with GAD chooses drug treatment, offer an SSRI. Consider offering sertraline first because it is the most cost-effective drug, but note that at the time these recommendations were published (March 2012) sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Monitor the person carefully for adverse reactions. If sertraline is ineffective, offer an alternative SSRI or an SNRI, taking into account the following factors:

- tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine)
- side-effect profile and potential for drug interactions
- the risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine)
- the person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference).

If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin.

Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises.

Do not offer an antipsychotic for the treatment of GAD in primary care.

STEP 4

This step normally refers to community mental health teams but may include specialist services and specialist practitioners in primary care.

Assessment

Offer the person a specialist assessment of needs and risks, including:

- duration and severity of symptoms, functional impairment, comorbidities, risk to self and self-neglect
- a formal review of current and past treatments, including adherence to previously prescribed drug treatments and the fidelity of prior psychological interventions, and their impact on symptoms and functional impairment
- home environment
- support in the community
- relationships with and impact on families and carers.

Review the needs of families and carers and offer an assessment of their caring, physical and mental health needs if one has not been offered previously.

Develop a comprehensive care plan in collaboration with the person with GAD that addresses needs, risks and functional impairment and has a clear treatment plan.

Treatment

Inform people with GAD who have not been offered or have refused the interventions in steps 1–3 about the potential benefits of these interventions, and offer them any they have not tried.

Consider offering combinations of psychological and drug treatments, combinations of antidepressants or augmentation of antidepressants with other drugs, but exercise caution and be aware that:

- evidence for the effectiveness of combination treatments is lacking and
- side effects and interactions are more likely when combining and augmenting antidepressants.

Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested.

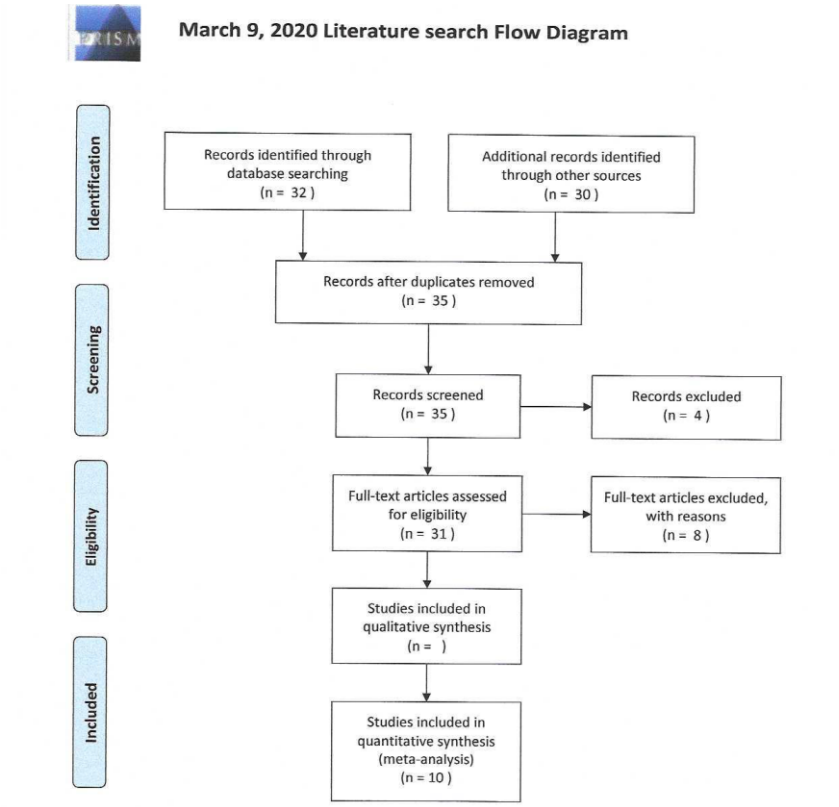
Appendix B: Clinical and economic evidence identification

Company search strategy, screening criteria and process for clinical evidence

A literature search was performed using 3 resources (Google Scholar, PuMed and PuMed Central) to include the period from 1st January 1981 to 9th March 2020. Search terms were: “anxiety” “Alpha-Stim,” “CES,” “electrotherapy,” “cranial electrotherapy stimulation”. The terms anxiety, electrotherapy, CES, and cranial electrotherapy stimulation were paired with the term “Alpha-Stim” to limit findings to the device in question. In addition, the company’s own website was searched.

Exclusion criteria: CES devices that were not Alpha-Stim; Inclusion criteria: studies utilizing Alpha-Stim technology. Screened abstracts of returned articles to investigate for inclusion or exclusion criteria. Articles that were not excluded when the abstract was screened were read more carefully for inclusion or exclusion.

Company study selection for clinical evidence



Company search strategy for adverse events

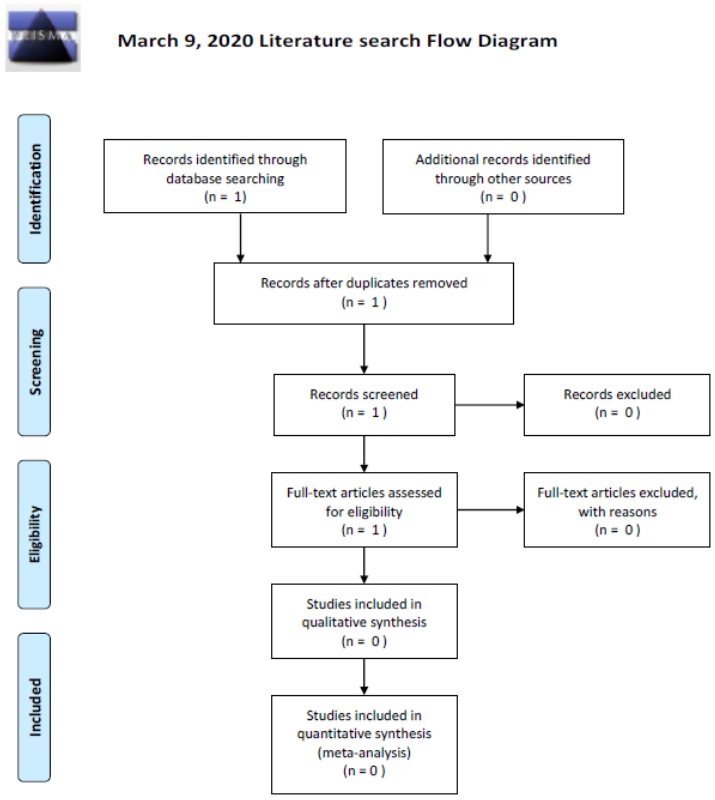
The company searched the MHRA and FDA MDR and MAUDE databases for information published between 1st January 1980 and 27th March 2020 using the term “Alpha-Stim”. No records were identified in the MHRA databases and 2 records were identified in MAUDE. In addition, the company’s own records of adverse events were searched. All adverse reactions identified from all sources were included in the company submission.

Company search strategy, screening criteria and process for economic evidence

A literature search was performed using 3 resources (Google Scholar, PuMed and PuMed Central) to include the period from 1st January 1981 to 9th March 2020. Search terms were: “anxiety” “Alpha-Stim,” “CES,” “electrotherapy,” “cranial electrotherapy stimulation”, “economics”. The terms anxiety, electrotherapy, CES, economics, cost and cranial electrotherapy stimulation were paired with the term “Alpha-Stim” to limit findings to the device in question. In addition, the company’s own website was searched.

Exclusion criteria: CES devices that were not Alpha-Stim; Inclusion criteria: studies utilizing Alpha-Stim technology and comparing cost-effectiveness of treating the device. Screened abstracts of returned articles to investigate for inclusion or exclusion criteria. Articles that were not excluded when the abstract was screened were read more carefully for inclusion or exclusion.

Company study selection for economic evidence



EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. The company's search strategy was simplistic using only free text terms (no Medical Subject Headings) and searching a limited selection of resources. The EAC considered there was a risk of not identifying all the relevant literature; however, the EAC note that the company host an online bibliography of relevant Alpha-Stim research and therefore it is likely that all relevant research evidence was identified. To ensure that all relevant research had been identified the EAC conducted its own systematic search, to include periods from 1st January 1980 to the 12th May 2020. Nine bibliographic databases and one clinical trial registry were searched using a range of free text terms and (where appropriate) subject headings; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
12/05/2020	Cochrane Library (Wiley) CDSR CENTRAL	 0 relevant 64	
12/05/2020	CRD databases: DARE HTA NHS EED	 2 duplicate Cochrane reviews 0 0	
12/05/2020	EMBASE (Ovid)	60	
12/05/2020	Medline ALL (Ovid) – includes Medline In Process & Medline Epub Ahead of Print)	194	
12/05/2020	PubMed	6	
12/05/2020	Scopus (Elsevier)	37	
12/05/2020	Web of Science (Clarivate Analytics)	31	
12/05/2020	MHRA – search of MDA & FSN	0	
19/05/2020	MAUDE adverse events	3	
12/05/2020	Records from manufacturer website	17	
			285
12/05/2020	Clinicaltrials.gov	1 – not imported as not ICD-11 'anxiety related disorder'	
24/06/2020 (later dated search as website was unavailable due to COVID-19 traffic)	WHO ICTRP	8 – not imported as 2 were duplicates, 1 completed but no analysis of 7 participants, 1 completed but no results, 1 not ICD-11 'anxiety related disorder', 3 terminated	

Search strategies

Cochrane Library

ID Search Hits

#1 ("alpha-stim" or "electrotherapy stimulation"):ti,ab,kw (Word variations have been searched) 52

#2 MeSH descriptor: [Electric Stimulation Therapy] this term only 1838

#3 #1 or #2 1873

#4 (anxiety):ti,ab,kw (Word variations have been searched) 47694

#5 MeSH descriptor: [Anxiety Disorders] explode all trees and with qualifier(s): [therapy - TH] 2288

#6 #4 or #5 48336

#7 #3 and #6 66

Note: 2 reviews and 64 trials, reviews not included as 1 was empty review and other was 'Non-pharmacological interventions for chronic pain in people with spinal cord injury'

CRD

Searched for: (alpha-stim or "electrotherapy stimulation") AND anxiety

---

EMBASE <1947-Present>

1 ("alpha-stim" or "electrotherapy stimulation").tw. (93)

2 electrotherapy/ (1454)

3 1 or 2 (1534)

4 anxiety.tw. (273988)

5 exp anxiety disorder/th [Therapy] (25736)

6 4 or 5 (289753)

7 3 and 6 (60)

8 limit 7 to yr="1980 -Current" (60)

Ovid MEDLINE(R) ALL <1946 to May 11, 2020>

1 ("alpha-stim" or "electrotherapy stimulation").tw. (73)

2 Electric Stimulation Therapy/ (20345)

3 1 or 2 (20373)

4 anxiety.tw. (185416)

5 exp Anxiety Disorders/th [Therapy] (15613)

6 4 or 5 (194422)

7 3 and 6 (223)

8 limit 7 to yr="1980 -Current" (194)

Pubmed

Searched for: alpha-stim

Scopus

(TITLE-ABS-KEY (anxiety) AND TITLE-ABS-KEY ("electrotherapy stimulation")) AND PUBYEAR > 1979

Web of Science

TS=(anxiety) AND TS=("electrotherapy stimulation" or alpha-stim)

Indexes=SCI-EXPANDED, CPCI-S Timespan=1980-2020

For MAUDE and MHRA

Searched for: alpha-stim

Clinicaltrials.gov

1 Study found for: alpha-stim AND anxiety | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies

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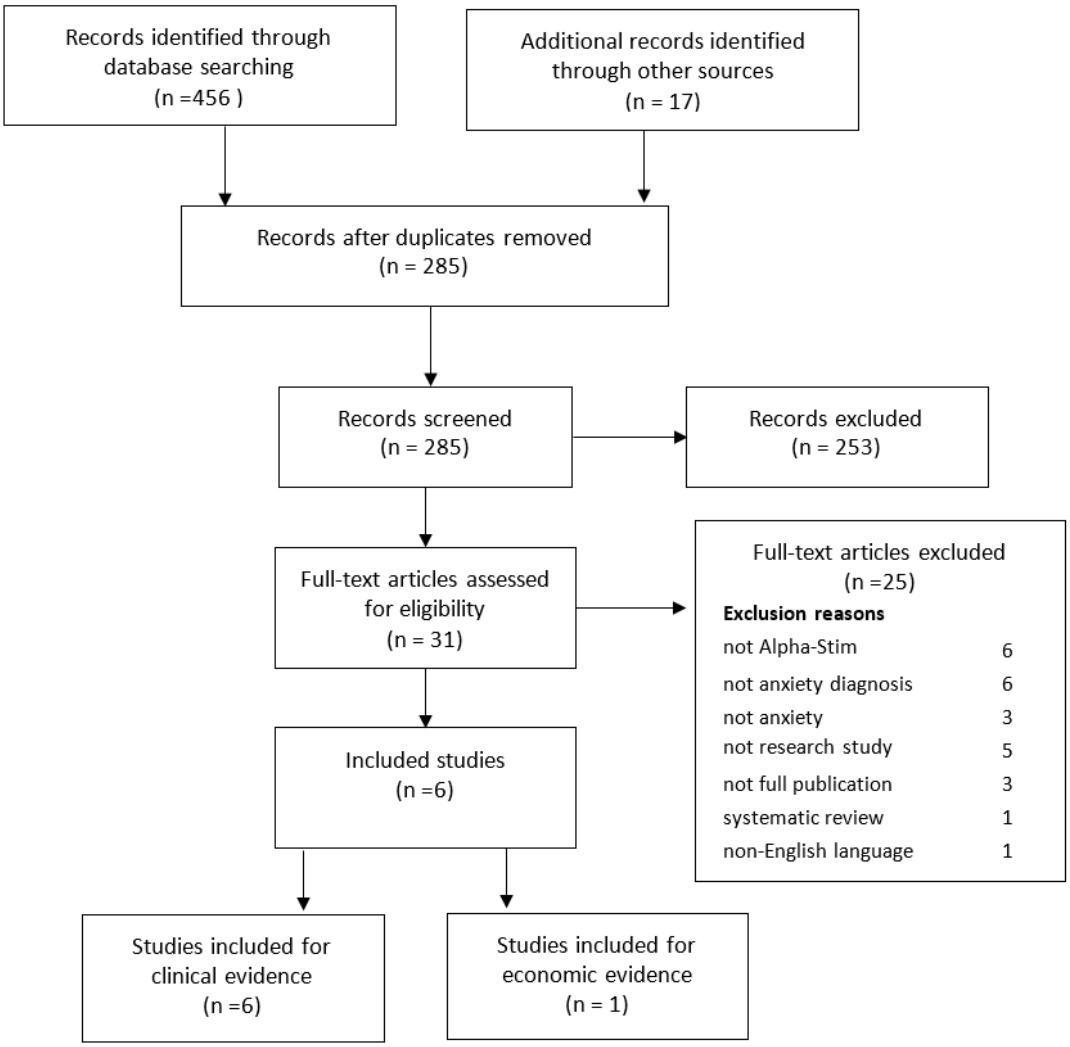
ICTRP

8 studies for: alpha-stim AND anxiety

EAC study selection



Appendix C: Table of EAC decisions on studies in company submission

Studies identified by company	EAC decision – eligibility for main results (Tables 4 and 7)	EAC decision – out of scope but contains potentially relevant data (Table 8)
Published Studies		
Barclay & Barclay (2014)	**Include**	N/A (main results)
Gibson & O'Hair (1987)	Exclude	**Include**
Gong (2016)	Exclude	Exclude
Kim (2008)	Exclude	Exclude
Kirsch (2014)	Exclude	**Include**
Kirsch (2019)	Exclude	Exclude
Koleoso (2013)	Exclude	**Include**
Lee (2013)	Exclude	Exclude
Libretto (2015)	Exclude	**Include**
Lichtbroun (2001)	Exclude	Exclude
Lu & Hu (2014)	**Include**	N/A (main results)
Morriss (2019)	**Include**	N/A (main results)
Morrow (2019)	Exclude	Exclude
Overcash (1999)	**Include**	N/A (main results)
Winick (1999)	Exclude	**Include**
Yennurajalingam (2018)	Exclude	**Include**
Cork (2014)	Exclude	Exclude
Lande & Gradnani (2018)	Exclude	Exclude
Mellen & Mackey (2009)	Exclude	Exclude
Mellen & Mackey (2008)	Exclude	Exclude
Platoni (2019)	Exclude	Exclude
Abstracts		
Price (2013)	Exclude	Exclude
Ongoing or unpublished studies		
Royal (2020-)	Exclude	Exclude
Voris (1995)	**Include**	N/A (main results)
Excluded by company		
Bystritsky (2008)	**Include** – meets scope	N/A (main results)
Chen (2007)	Exclude – out of scope	**Include**
Hill (2015)	Exclude - unpublished (not checked)	Exclude
Lu (2005) *2006 in company submission*	Exclude – out of scope	Exclude
Lyon (2015)	Exclude – out of scope	Exclude
Mellen (2016)	Exclude - out of scope (not checked)	Exclude
Rickabaugh (2016)	Exclude - unpublished (not checked)	Exclude
Strentzsch (2008)	Exclude - unpublished (not checked)	Exclude

Appendix D: Critical appraisal of clinical evidence

Quality assessment of included controlled trials (n=3) assessed by the Cochrane Risk of Bias tool (Sterne et al. 2019)

Risk of Bias Domain	Barclay & Barclay (2014)	Lu & Hu (2014)	Voris (1995) Unpublished
Bias arising from the randomization process	Some concerns	Some concerns	Some concerns
Bias due to deviations from intended interventions	Some concerns	Some concerns	Some concerns
Bias due to missing outcome data	Low	Low	High
Bias in measurement of the outcome	High	Low	Low
Bias in selection of the reported result	Low	Some concerns	Some concerns
Overall risk of bias	**High**	**Some concerns**	**High**

Overall risk-of-bias judgement graded as: 'low' risk of bias if low risk of bias for all domains; 'some concerns' if some concerns in at least one domain but not to be at high risk of bias for any domain; 'high' risk of bias if high risk of bias in at least one domain or 'some concerns' for multiple domains in a way that substantially lowers confidence in the result.

Quality assessment of included Before and After studies (n=3) assessed by the NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (National Heart, Lung, and Blood Institute, 2014)

Criteria	Bystritsky et al. (2008)	Morriss et al. (2019)	Overcash (1999)
1. Was the study question or objective clearly stated?	Yes	Yes	Yes
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	NR
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	Yes	Yes	CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Yes	Yes but high number of eligible patients declined to participate (78%)	CD
5. Was the sample size sufficiently large to provide confidence in the findings?	No – only 12 (pilot study)	Yes (sample size calculation described)	Yes but no sample size calculation
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	Yes	Yes	Yes

7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes – HAM-A (although not clear whether clinician-administered or self-reported)	Yes (GAD-7 questionnaire that is self-administered)	No – comparison of 3 objective physiological measures and one subjective measure. No validated questionnaire used such as HAM-A.
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	NR (unlikely as single-arm study)	No – study was open label and patient self-reported scores	No – subjective measure as self-report and not clear for objective measures
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	No – 25% loss to follow-up but ITT analysis	No – 30% loss to follow-up but ITT	Yes 8% loss to follow-up but no ITT
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	Yes (LOCF used which may be problematic)	Yes (missing data imputed)	Yes
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	No	No
Overall Rating	**Poor**	**Poor**	**Poor**

*CD, cannot determine; NA, not applicable; NR, not reported

Appendix E: Studies included by company and excluded by the EAC

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Cork et al. (2004) USA	**Design:** Double blind, cross-over study with random allocation. **Intervention:** Alpha-Stim CES device, pre-set to provide 1 hour at 100 µA. Frequency not reported. 3 weeks of treatment then cross-over (n=39). **Control:** Sham device with no current (n=35). 🟢	**Participants:** Adults with fibromyalgia. No anxiety symptoms reported. **Setting:** Pain clinic in USA 🔴	Pain intensity McGill Pain Score Tenderpoint score Profile of Mood States (POMS) Oswestry Score 🔴	**Out of scope based on population.** No diagnosis of anxiety disorder or symptoms of anxiety. **Out of scope based on outcomes.** No anxiety-specific outcomes.
Gong et al. (2016) China	**Design:** Open-label, prospective RCT with 4 week run-in **Intervention:** Alpha-Stim SCS set to sub-perception threshold 30 minutes each time, and biofeedback therapy (5 times a week, 10 times per course, 3 courses total). (n=38) **Control:** Biofeedback therapy only (n=36) 🟢	**Participants:** Patients with functional constipation. No anxiety symptoms or diagnosis reported. **Setting:** Pelvic floor centre at Hospital in China 🔴	Self-rating anxiety scale Self-rating depression scale Wexner constipation score 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or symptoms of anxiety.
Kim et al. (2008) Korea	**Design:** investigator-blinded, RCT. **Intervention:** Alpha-Stim (model not reported) fixed below 200 µA, 0.5 Hz for 20 mins in pre-surgical waiting area (n=30). **Control:** Supportive nursing care (n=30) 🟢	**Participants:** Adults awaiting surgery under general anaesthesia. No anxiety symptoms or diagnosis reported. **Setting:** Hospital in South Korea 🔴	Anxiety scale 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or symptoms of anxiety.

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Kirsch et al. (2019) USA	**Design:** Prospective, single arm cohort study. **Intervention:** Alpha-Stim (model not reported) at a comfortable current level for 20-60 minutes daily at 0.5 Hz. (n=35). **Control:** None 🟡	**Participants:** Healthy volunteers (teachers) who responded to flyers and newsletter announcements. Financial incentives available. No anxiety symptoms or diagnosis reported. **Setting:** Not reported. 🔴	Pre and post-treatment measures were recorded on a 0-10 scale for any or all subjective changes in anxiety, depression, insomnia, and pain. 🟢	**Out of scope based on population.** Healthy volunteer teachers with no diagnosis of an anxiety disorder or anxiety symptoms required. **Possibly out of scope based on intervention.** The purpose of this study was to examine the effectiveness of monitoring the progress of Alpha-Stim CES treatments using a smartphone application ("app").
Lande & Gragnani (2018) ABSTRACT ONLY USA	**Design:** Open label, prospective, convenience sample study. **Intervention:** 20 minutes of CES at comfortable level (n=50). Device not reported. **Control:** None 🔴	**Participants:** Active duty service members receiving treatment. **Setting:** Psychiatry Continuity Service, Walter Reed National Military Medical Center in Bethesda, Maryland 🔴	qEEG changes Subjective Units of Distress Scale (SUDS) 🟢	**Out of scope due to population.** Not reported whether patients had diagnosis of anxiety disorder. **Possibly out of scope due to intervention**. Not confirmed if intervention device is Alpha-Stim. Abstract only.
Lee et al. (2013) Korea	**Design:** Prospective, blinded, randomised. **Intervention:** Alpha-Stim 100. 20 mins on day before and day of surgery (100 μA, 0.5 Hz). (n=25) **Control:** Sham device with no current. (n=25) 🟢	**Participants:** Female patients undergoing thyroidectomy. No anxiety symptoms or diagnosis reported. **Setting:** Department of Anesthesiology and Pain Medicine, Ansan Hospital of Korea 🔴	Anxiety score Pain score Serum adrenocorticotropic hormone (ACTH), cortisol and blood glucose levels 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms.

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Lichtbroun et al. (2001) USA	**Design:** Double blind, sham device controlled study with random assignment to groups. (n=60 in total) **Intervention:** Alpha-Stim device (model not reported) present to provide 1 hour of 100 μA at 0.5 Hz, every day for 3 weeks (n=not reported) **Controls:** Sham device with no current or wait in line (n=40) 🟢	**Participants:** Adults with fibromyalgia. No anxiety symptoms or diagnosis reported. **Setting:** A large fibromyalgia clinic in USA. 🔴	Self-ratings of pain, sleep, well-being, quality of life. Profile of mood state (POMS) 🔴	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms. **Out of scope based on outcomes.** No anxiety-specific outcomes.
Mellen & Mackey (2008) USA	**Design:** Single arm, pilot study. Possibly the same sample as Mellen & Mackey (2009). **Intervention:** Alpha-Stim SCS, 20 sessions of 20 minutes in length with present intensity. (n=not reported) **Control:** None 🟡	**Participants:** Officers from the sheriff's staff. No eligibility criteria reported or patient demographics. No anxiety symptoms or diagnosis reported. **Setting:** Not reported 🔴	Brief symptom inventory (BSI) Beck depression inventory (BDI) Beck Anxiety Inventory (BAI) Global Severity index (GSI) Positive symptom total (PST) Positive symptom distress index (PSDI) 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms.

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Mellen & Mackey (2009) USA	**Design:** Blinded controlled study with random allocation. **Intervention:** Alpha-Stim SCS set at 10 μA for 20 minutes and for 20 sessions. (n=not reported) **Control:** Sham device with non therapeutic level of current. (n=not reported) n=21 volunteers in total.	**Participants:** Volunteer officers from the sheriff's staff. No anxiety symptoms or diagnosis reported. **Setting:** Not reported.	Brief symptom inventory (BSI) Beck depression inventory (BDI) Beck Anxiety Inventory (BAI) Global Severity index (GSI) Positive symptom total (PST) Positive symptom distress index (PSDI)	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms.

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Morrow et al. (2019) USA	**Design:** Retrospective, non-comparative cohort study on veterans who completed valid treatments of Alpha-Stim or Laser Touch One **Intervention:** Alpha-Stim M 5 days a week for 2 weeks (veteran must have attended at least 8 sessions) (n=91). **Control:** None 🟡	**Participants:** Veterans who have chronic or persistent pain (≥ 3 months) that interferes with function or quality of life are considered good candidates for a device trial if they are actively involved in pain self-care, logistically able to participate, able to use a device long-term, and have no contraindications. No anxiety symptoms or diagnosis reported. **Setting:** Pain clinic in the US for veterans. Each participating veteran takes part in a device trial to confirm that he or she is able to use the recommended device independently and is likely to benefit from its use. Veterans who do not respond to the initial device trial could test the potential benefit of another device. 🔴	Beck Depression Inventory (BDI-II) Beck Anxiety Inventory (BAI) Pain Catastrophizing Scale (PCS) Subjective Units of Distress Scale (SUD) Brief Pain Inventory (BPI) 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms.
Price et al. (2013) UNPUBLISHED	**Design:** Mail survey sent out by manufacturer with warranty card for device (post-marketing surveillance). Possibly results from multiple merged surveys (unclear in reporting). **Intervention:** Alpha-Stim (model not reported) and no details available on protocol of use. Mean duration of use was 1 month. 🟡	**Participants:** Survey included civilians, service members and veterans. No anxiety symptoms or diagnosis reported. **Setting:** Post-marketing surveillance survey. 🔴	Self-rated anxiety, insomnia, depression and PTSD. 🟢	**Out of scope based on population.** No confirmed diagnosis of anxiety disorder. Not enough methodological detail in unpublished report to carry out critical appraisal.

Study name and location	Design, intervention(s), sample size	Participants & setting	Outcomes	EAC comments
Platoni et al. (2019) USA	**Design:** Single-arm, before-after, cohort study. Unclear if prospective or retrospective. **Intervention:** Alpha-Stim (model not reported) used at comfortable level (100-600 μA) at 0.5 Hz for 20-60 minutes daily. Length of study was 6 weeks (n=86). **Control:** None 🟡	**Participants:** Self-selecting group of first responders from US. No eligibility criteria or description of how participants were identified. No anxiety symptoms or diagnosis reported. **Setting:** Not reported. 🔴	Perceived level of anxiety, insomnia, depression, and pain recorded on smartphone app. 🟢	**Out of scope based on population.** No diagnosis of anxiety disorder or anxiety symptoms.
Royal et al. (UNPUBLISHED)	No methodological information available other than that reported in company submission. 🔴	No methodological information available other than that reported in company submission. 🔴	No methodological information available other than that reported in company submission. 🔴	**Out of scope due to status.** No methodological information available other than that reported in company submission. Raw results kindly provided by author. But not enough information to assess eligibility for inclusion.
🟢🟡🔴 Green, amber, red colour coding indicates whether the study matches the scope of the assessment fully, partially, or not at all, respectively.				

Appendix F: Adverse event data

Company adverse event data from included studies

Study	Design and intervention(s)	Details of adverse events	Company comments
Morris (2019)	Open label Alpha-Stim CES	Mild headache - 2; nausea - 1; "strange feeling after use" - 1.	All reported adverse events were mild. Headaches and nausea are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Morrow (2019)	Open Label Alpha-Stim CES	Headache - 3	All reported adverse events were mild. Headaches are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Gong (2016)	Open Label Alpha-Stim CES	Tingling in the ears at the site of the earclips – 3; earclips feeling too tight – 2; drowsiness - 1	All reported adverse events were mild. Drowsiness is known possible effect and usually occurs when treatment is stopped too soon. Continuing treatment for a few additional minutes will alleviate the feeling of drowsiness. Feelings of "tingling" at the site of the earclips is a normal aspect of CES treatment and is not harmful.
Amr (2013)	Open Label Alpha-Stim CES	Mild dizziness - 4	All reported adverse events were mild. Dizziness is a known possible effect and usually occur when the current is set too high for the patient. It is usually are mild and self-limiting.
Tan (2011)	RCT Alpha-Stim CES	Alpha-Stim® CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 12; Legs, tingling. burning,	All reported adverse events were mild. Tingling at the site of the earclips is a

		electric shot in feet – 1; Spasms, leg spasms – 1; Burning in buttocks – 1; Ringing in ears – 1; Drowsy, sleepy, fell asleep, relaxing – 7; Dizzy, lightheaded, feeling crooked – 3; Nausea, stomach rolled – 1; Headache, slight headache – 2; Metallic or unusual taste in mouth – 1; Increased pain – 1. Sham CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 6; Head tingles – 1; Legs tingling, electric shot in feet – 1; Spasms, leg spasms – 2; Drowsy, sleepy, fell asleep, relaxing – 4; Dizzy, lightheaded, feeling crooked – 1; Nausea, stomach rolled – 2; Shaky – 1; Heart racing, chest pain – 2; Headache, slight headache – 3; Metallic or unusual taste in mouth – 1; Increased pain – 1.	normal aspect of CES treatment and is not harmful. Headache, nausea, dizziness and drowsiness are known possible effects and usually occur when the current is set too high for the patient. The sensations of burning, tingling, or spasms is likely attributable to the population studied and the aim of the study to treat neuropathic pain with CES.
Rintala (2010)	RCT Alpha-Stim CES	Alpha-Stim® CES group: Pulsing, tickling, tingling in ears – 3; Tender ears – 1; Pins and needles sensation in bladder – 1. Sham CES group: Drowsiness – 1; Warm ears – 1; Headache – 1.	All reported adverse events were mild. Pulsing and tingling sensation at the earclip site is a normal aspect of CES treatment and is not harmful. Participants were being treated for Parkinson's Disease, which may account for "pins and needles sensation in bladder" reported by one participant.
Eidelman (2009)	Open label Alpha-Stim CES	Vertigo - 3	All reported adverse events were mild. Vertigo is a known possible effect and usually occurs when the current is set too high for the patient.
Mellen (2009)	RCT Alpha-Stim CES	Agitation – 1	The reported agitation was mild and self-limiting. Although extremely rare, this type of paradoxical effect is a known possibility of CES treatment.
Bystritsky (2008)	Open label Alpha-Stim CES	Dizziness – 2; headache - 1	All reported adverse events were mild. Headaches and dizziness are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.

Strentzch (2008)	RCT Alpha-Stim CES	Alpha-Stim® CES Group: One subject from the active CES group reported increased auditory hallucinations but remained in the study with no further problems (p. 56). Sham CES Group: Two subjects from the sham group reported headaches from treatment (p. 56).	All reported adverse events were mild. The reported headaches were in the sham group and therefore not related to CES treatment. The increased hallucinations occurred in a psychiatric patient with a history of hallucinations and unlikely to be related to the CES treatment.
Lu (2005)	Open label Alpha-Stim CES	Dizziness and some irritation at site of earclips - 3	All reported adverse events were mild. Dizziness and skin irritation at the electrode site are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Kirsch (2002)	Survey Alpha-Stim CES	Dizziness – 6; nausea – 2; skin irritation – 3; heavy feeling – 1; anger – 1; metallic taste – 1; intensified tinnitus – 1.	All reported adverse events were mild. Nausea, skin irritation, and dizziness are known possible effects and usually occur when the current is set too high for the patient. A heavy feeling is also a known effect and can occur when treatment is stopped too soon. Paradoxical effects such as anger and increased tinnitus are extremely rare, but known effects that are mild and self-limiting.

Adverse event data extracted by EAC from included studies

Study name	Barclay & Barclay (2014)	Bystritsky et al. (2008)	Morriss et al. (2019)	Overcash (1999)	Lu & Hu (2014)
	No participant reported any adverse events verbally or in their treatment log during the study.	3 patients discontinued treatment after baseline due to adverse events including dizziness (n=2) and headache (n=1).	4 (2.5%) patients withdrew because of side effects (2 headaches and insomnia, 1 nausea, and 1 strange feeling after use),	Not reported.	Not reported

Appendix G: EAC critique of company meta-analysis

The EAC have not undertaken a full critical appraisal of the meta-analysis. However, the EAC have noted some particular limitations with the reported methodology, including:

There is not enough information given to follow the quality assessment process undertaken of the included studies. The company submission only states that the studies were all categorised as “good” which means 0-1 limitations. The EAC would not agree with this assessment and would expect more limitations to be recorded.

The company has not described the eligibility criteria for selection of studies into the meta-analysis.

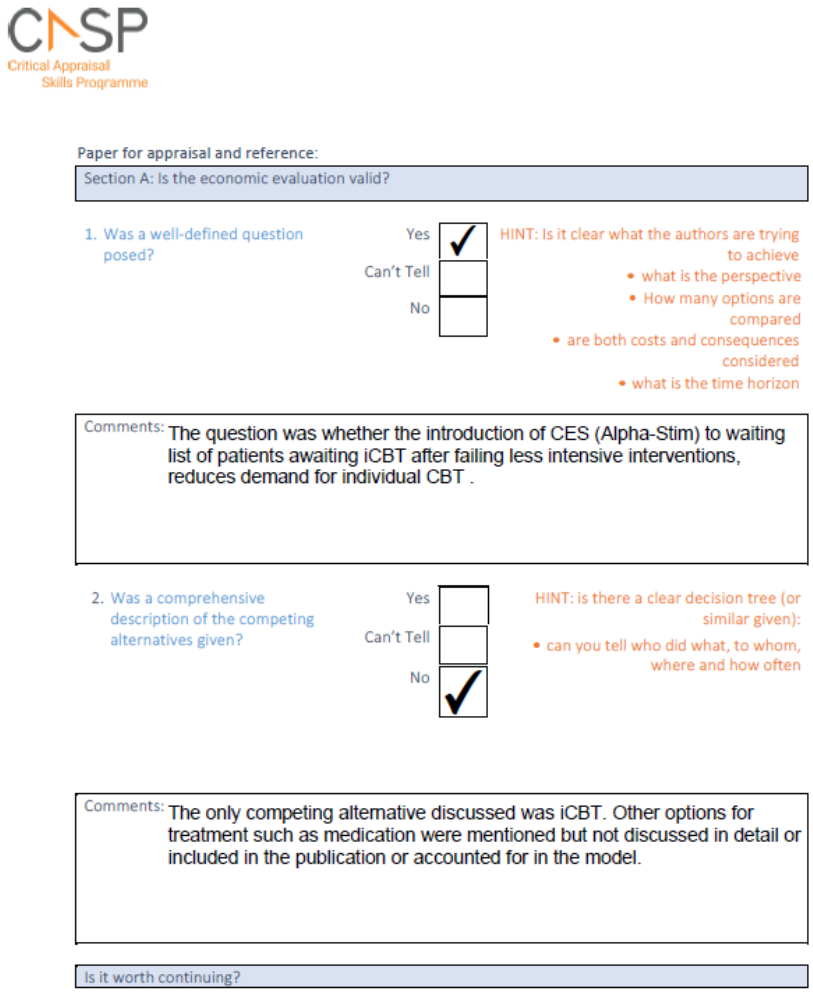
The company has not described the included studies themselves (population, intervention (model of Alpha-Stim), control, outcomes, setting) and the PRISMA diagram does not describe the selection of studies for the meta-analysis.

The company has not adequately commented on differences in the study design. There are important differences in the population, comparators, and outcome

No description has been given of how the effect size was calculated from the data in each of the included studies.

Appendix H: Checklist for critical appraisal of economic studies

CASP Economic Evaluation checklist used to undertake critical appraisal of Morriss et al. (2019)



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Paper for appraisal and reference:

Section A: Is the economic evaluation valid?

1. Was a well-defined question posed?

Yes	✓
Can't Tell	
No	

HINT: Is it clear what the authors are trying to achieve
- what is the perspective
- How many options are compared
- are both costs and consequences considered
- what is the time horizon

Comments: The question was whether the introduction of CES (Alpha-Stim) to waiting list of patients awaiting iCBT after failing less intensive interventions, reduces demand for individual CBT .

2. Was a comprehensive description of the competing alternatives given?

Yes	
Can't Tell	
No	✓

HINT: is there a clear decision tree (or similar given):
- can you tell who did what, to whom, where and how often

Comments: The only competing alternative discussed was iCBT. Other options for treatment such as medication were mentioned but not discussed in detail or included in the publication or accounted for in the model.

Is it worth continuing?

2

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3. Does the paper provide evidence that the programme would be effective? (i.e. would the programme do more good than harm?)

Yes	
Can't Tell	✓
No	

HINT: Consider:
- if an RCT or systematic review was used; if not, consider how strong the evidence was (economic evaluations frequently have to integrate different types of knowledge stemming from different study designs)

Comments: The model is a simple decision tree model making a direct comparison between 2 treatment pathway options Alpha-Stim to 1st line iCBT to 2nd line iCBT versus 1st line iCBT to 2nd line iCBT only. Results suggest that Alpha-Stim would be effective however the clinical data on which the response rates are based is poor quality.

4. Were the effects of the intervention identified, measured and valued appropriately?

Yes	
Can't Tell	✓
No	

HINT: Effects can be measured in natural units (e.g. years of life) *or* more complex units (e.g. years adjusted for quality of life such as as QALYS) *or* monetary equivalents of the benefit gained (e.g. $)

Comments: Efficacy of Alpha-Stim (consequences) was measured based on changes in GAD scores which is a clinically acceptable/appropriate approach however the model assumes only one, 24 week cycle of treatment and does not address the possibility of cycles of relapse-remmission which have been highlighted by clinical experts as the natural pathway for patients with anxiety disorders.

Costs for Alpha-Stim device and iCBT sessions are reported in monetary units

Section B: How were consequences and costs assessed and compared?

5. Were all important and relevant resources required, and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?

Yes	
Can't Tell	
No	✓

HINT: Identified?
- remember the perspective being taken

HINT: measured accurately?
- appropriate units may be hours of nursing time, number of physician visits, years-of-life gained etc.

HINT: valued credibly?
- are the values realistic
- how have they been derived
- have opportunity costs been considered

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Comments: Resources
Cost of Alpha-Stim per patient in the model assumes that 100% of patients who are offered Alpha-Stim while on the waiting list will accept and use it. There will be a cost to purchasing the Alpha-Stim device and if patients don't use it, the cost per-patient use for the device will be higher.
Cost of iCBT is taken from published literature with a single cost per hour of iCBT. Three models of CBT were detailed with different costs.

No additional resource use costs were included (e.g. additional GP appointments for patients using Alpha-Stim while on the waiting list; medication/prescription costs)

EQ-5D responses have been reported however as the study had no direct comparator, no utility values have been reported and no attempt has been made to source comparator utilities from the literature.

6. Were costs and consequences adjusted for different times at which they occurred (discounting)?

Yes	
Can't Tell	
No	✓

Comments: No discounting applied due to short time horizon of the model
Time horizon only accounts for one cycle of treatment - no relapse/remission cycles

7. What were the results of the evaluation?

Yes	
Can't Tell	
No	

HINT: Consider
- what is the bottom line
- what units were used (e.g. cost/life year gained, cost/QALY, net benefit)

Comments: The results of the model suggest that Alpha-Stim is cost-saving compared with iCBT due the lower cost of Alpha-Stim per-patient and a reduction in numbers of patients going on to receive iCBT after treatment with Alpha-Stim

8. Was an incremental analysis of the consequences and cost of alternatives performed?

Yes	
Can't Tell	
No	✓

Comments:

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9. Was an adequate sensitivity analysis performed?

Yes	
Can't Tell	✓
No	

HINT: Consider
- if all the main areas of uncertainty were considered by changing the estimate of the variable *and*
- looking at how this would change the result of the economic evaluation

Comments: A probabilistic sensitivity analysis was performed however there is not enough information reported to adequately critique the analysis.

One deterministic sensitivity analysis was performed on cost of Alpha-stim to identify the threshold at which is become cost-incurring.

Section C: Will the results help in purchasing for local people?

10. Is the programme likely to be equally effective in your context or setting?

Yes	
Can't Tell	✓
No	

HINT: Consider whether
- the patients covered by the review could be sufficiently different to your population to cause concern
- your local setting is likely to differ much from that of the review

Comments: The clinical pathway for treatment of anxiety is more complex than that represented by the decision tree.

11. Are the costs translatable to your setting?

Yes	
Can't Tell	✓
No	

Comments: The costs and subsequent cost-savings calculated are likely to be impacted by a number of factors which have not been considered in this model.

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12. Is it worth doing in your setting?		
	Yes	
	Can't Tell	✓
	No	

Comments: The quality of the clinical data is poor which has an impact on the outcome of the economic analysis. Alpha-stim shows some promise for clinical effectiveness suggesting therefore that an economic analysis is of value although caution is advised when interpreting the results

Appendix I: Model Behaviour Testing by EAC

Model behaviour testing				
Test	**Intervention cost (Alpha-Stim)**	**Comparator cost (iCBT)**	**Difference**	**EAC Comment**
	£753.36	£1,294.23	-£540.88	Company submission gives costs for the total cohort. EAC calculated the cost per patient by dividing total cohort cost by 1,000 to give a per-patient cost.
Patient Cohort				
Set patients to '0' Worksheet: Executive Summary Cell: H5				Expected costs reset to zero PSA costs reset to zero Values adjust accordingly for all 3 treatment choices Expected result – no patients in the cohort means no costs incurred
Set patients to '2,000' Worksheet: Executive Summary Cell: H5				Expected costs double but incremental cost saving remains the same PSA costs adjust accordingly Values adjust accordingly for all 3 treatment choices Expected result – total costs will increase with more patients but the increase affects both arms equally so no change in incremental cost
Intervention/Comparator Costs				
Set cost of Alpha-Stim to £0 Worksheet: Cost Inputs Cell: F26	£683.35	£1,294.23	-£610.38	Cost of Alpha-Stim reduces to £0 which reduces the cost of the Alpha-Stim arm by £70 Incremental cost savings with Alpha-Stim increase. Expected result – total cost of treatment in the Alpha-Stim arm is reduced so incremental cost saving increases

Set Alpha-Stim cost to £5,000 Worksheet: Cost Inputs Cell: F26	£1,683.35	£1,294.23	£389.12	Cost of Alpha-Stim increases to £1,000 per patient Incremental costs change accordingly Expected result: total cost of treatment in the Alpha-Stim arm increases and Alpha-Stim becomes cost incurring.
Set cost of a low intensity iCBT session to £0 Worksheet: Cost Inputs Cell: J6	£70	£0	£70	Cost of iCBT is removed from the standard care model reducing the costs for both arms Cost of Alpha Stim remains the same For the Clark and Wells model and Heimberg model, the cost of iCBT is reduced as expected but there are still iCBT costs associated (high intensity sessions) Sensitivity analysis cannot run with a value of £0 but setting a cost of £0.01 allows it to run Expected result: removal of iCBT cost results in Alpha-Stim becoming cost incurring
Number of patients per Alpha-Stim Device				
Set number of patients per Alpha-Stim device to 1 Worksheet: Cost Inputs Cell: F27	£753.35	£1,294.23	-£540.88	Reducing the number of patients per Alpha-Stim device does not impact the incremental costs Reducing the number of patients to 1 reduces the cost per Alpha-Stim Unit to £70 which maintains a £70 cost per patient (£70 unit cost/1 user) Unexpected result: reducing the number of patients per device should not impact the cost of the Alpha-Stim unit, it should increase the cost per patient of Alpha-Stim

Set number of patients per Alpha-Stim device to 50 Worksheet: Cost Inputs Cell: F27	£753.35	£1,294.23	-£540.88	Increasing the number of patients per Alpha-Stim device does not impact the incremental costs Increasing the number of patients to 50 increases the cost per Alpha-Stim Unit to £3,500 which maintains a £70 cost per patient (£3,500 unit cost/50 users) Unexpected result: increasing the number of patients per device should not impact the cost of the Alpha-Stim unit, it should reduce the cost per patient of Alpha-Stim
Number of iCBT treatment sessions				
Set number of standard care sessions to 1 Worksheet: Cost Inputs Cell: C19	£155.41	£161.79	-£6.36	Reducing the number of CBT sessions in the standard care model reduces the costs for both arms. No change to Clark and Wells Model or Heimberg Model Expected Result: any change made to number of sessions should impact the only the model (e.g. standard of care) in which those changes are made Note: The model also functions as expected when changing the number of sessions in the Clark and Wells model and Heimberg models. Changes made in one, do not impact the other two models.
Alpha-Stim Response Rates				
Set Alpha-Stim response rate to 99% Worksheet: Parameters Cell: G8	£82.94	£1294.23	-£1211.29	Increasing the probability of a response with Alpha-Stim reduces the number of patients who go on to receive CBT. No impact on the iCBT arm

				Expected result: Overall cost for Alpha-Stim Arm is reduced. Incremental cost savings increase
Set Alpha-Stim response rate to 1% Worksheet: Parameters Cell: G8	£1351.29	£1294.23	£57.06	Reducing the Alpha-Stim response increases the number of patients in the Alpha-Stim arm who go on to receive CBT No impact on the iCBT arm Expected result: Overall cost for Alpha-Stim Arm increases due to increase CBT. Incremental costs increase and Alpha-Stim becomes cost incurring
CBT Response Rates				
Set iCBT response rate to 99% Worksheet: Parameters Cell: G6	£543.38	£896.55	-£353.17	Increasing the response rate of iCBT reduces the overall cost in iCBT as fewer patients need a 2nd line of treatment. Alpha-Stim remains cost saving because there are still patients who incur cost of CBT but the incremental cost savings are reduced Expected result: increasing the response to CBT will reduce the need for further lines of CBT so reduce costs
Set iCBT response rate to 1% Worksheet: Parameters Cell: G6	£1002.70	£1766.48	-£763.78	Reducing the response rate of iCBT increases the overall cost in iCBT as more patients need a 2nd line of treatment. This increase also impacts the Alpha-Stim arm Incremental costs per patient increase in both arms but not as much in the Alpha-Stim arm Expected Result: reducing the response rates to iCBT means more patients 'fail' first line and

				move to second line iCBT increasing costs in both treatment arms. The increase in costs is greater in the iCBT arm meaning Alpha-Stim should become more cost saving as iCBT response rates reduce

Appendix J: EAC Corrections to Company Base case Model

Parameter	Company Value	EAC Value	Comment	Impact on Results
Cost of an Alpha-Stim device Worksheet: Cost Inputs Cell: F26	£350.00 (calculated using formula =70*F27)	£350 (entered as a value not a calculation)	The EAC identified during model stress testing the cost of an Alpha-Stim device was calculated using a formula which multiplied the cost per patient by the number of patients using the device. Similarly the cost per patient was then calculated using a formula to divide the cost of the device by the number of patients. This meant that changing the number of patients changed the cost of the Alpha-Stim device to maintain a £70 cost per patient use regardless of the number of patients expected to be using a single device. The change made by the EAC means that increasing the number of patients using the device does not change the cost of the Alpha-Stim device, it now adjusts the cost per patient use.	No Impact on base case point estimate Impact on the results of PSA – the cost of Alpha-Stim updates in the sensitivity analysis to reflect and increased or decreased number of patients using the device. The impact on the results of the PSA will be greater, the greater the change in cost of Alpha-Stim per patient.

Appendix K: Adjusted Company Base Case Assumptions

Assumption	EAC Comments
Number of patients using Alpha-Stim	
Cohort of 1000 patients with 22% using Alpha-Stim	Published literature suggests that only 22% will take up the offer of Alpha-Stim which means that a significant proportion of patients go straight to iCBT. Alpha-Stim The Alpha-Stim branch is modified as follows. 22% agree to use Alpha-Stim (cost of device + consumables) 78% decline to use Alpha-Stim and do not incur the cost of Alpha-Stim but go straight to iCBT (as an additional route to the company's model) and incur the cost of iCBT.
Response Rates	
Probability of Response to Individual CBT 0.542	
Probability of Response to Alpha-Stim 0.47	Response rate is the reported response rate in Morriss (2013).
Probability of response to iCBT remains the same for first and second cycles of iCBT	
Duration of Alpha-Stim Treatment	
Duration of Alpha-Stim treatment was 6 weeks with an option for a further 6 weeks (Morriss et al). Response was assessed at the end of a 12 week period and again at 24 weeks to assess degree of maintenance. Non-responders to Alpha-Stim would undergo iCBT as per the standard practice model.	
Duration of iCBT treatment	
Initial course of 8x60 minute sessions with non-responders undergoing a second course of 8X60 minute sessions.	
Cost of Alpha-Stim per patient	
Patients per Alpha-Stim life expectancy – 15 patients	There are is a lack of clarity in the company model with the way that the cost per patient has been calculated which have been checked with the company. The company has confirmed that the cost of Alpha-Stim is based on the cost of a device of £450 with 15 patients per device over the device lifetime (£30 per patient) plus additional cost of £40 per patient related to training, consumable, postage and therapist time, giving a total cost per patient of £70.
Cost of Alpha-Stim device - £450	

Proportion of patients using Alpha-Stim	
100% of the cohort will use Alpha-Stim	The company submission assumes 100% of patients incur the cost of Alpha-Stim and a reduced cost of iCBT based on 47.2% of the cohort responding to Alpha-Stim and not requiring further treatment. The EAC agrees with costing Alpha-Stim as £70 per patient using Alpha-Stim. The EAC however notes that as published literature suggests on 22% of patients will use Alpha-Stim, the EAC model assumes that 22% of the cohort will incur Alpha-Stim costs while the remaining 78% will move straight to iCBT. Patients who decline Alpha-Stim do not incur the cost of Alpha-Stim.
Cost of individual CBT	
60 min iCBT session - £112.49 90 min iCBT session - £201.93	Cost reported in Radhakrishnan uplifted to 2017/2018 costs – still looking into whether there is a better way to cost this. 1 Cycle of Standard Practice iCBT is 8*60min sessions (£899.92 per cycle)
Model of iCBT	
Standard Practice (8*60min sessions) for a maximum of 2 cycles	Validating this with the clinical experts at the moment

Appendix L: EAC Base Case Assumptions

Assumption	EAC Comments
Medication Use	
15% (0% to 30%) medication use as alternative treatment	A proportion of patients will chose medication over non-pharmacological treatments
50% (25% to 100%) medication use following non-response to Alpha-Stim/iCBT	A proportion of patients will choose medication use having tried non-pharmacological treatments with no response.
iCBT	
No second cycle of iCBT One cycle, 8 60 min sessions (2-20 sessions)	Clinical experts suggest that there is no second cycle of iCBT rather the patients receive a varying number of sessions depending on requirement.
Number of patients using Alpha-Stim	
Cohort of 1000 patients with 22% using Alpha-Stim	Published literature suggests that only 22% will take up the offer of Alpha-Stim which means that a significant proportion of patients go straight to iCBT. Alpha-Stim The Alpha-Stim branch is modified as follows. 22% agree to use Alpha-Stim (cost of device + consumables) 78% decline to use Alpha-Stim and do not incur the cost of Alpha-Stim but go straight to iCBT (as an additional route to the company's model) and incur the cost of iCBT.
Response Rates	
Probability of Response to Individual CBT 0.542 (0.433 to 0.650)	No change to point estimate. Range varied by 20%
Probability of Response to Alpha-Stim 0.47 (0.3776 to 0.5664)	Response rate is the reported response rate in Morriss (2013). No change to point estimate. Range varied by 20%
Cost of Alpha-Stim per patient	
Patients per Alpha-Stim life expectancy – 15 patients	There are is a lack of clarity in the company model with the way that the cost per patient has been calculated which have been checked with the company. The company has confirmed that the cost of Alpha-Stim is based on the cost of a device of £450 with 15 patients per device over the device lifetime (£30 per patient) plus additional cost of £40 per patient related to training, consumable, postage and therapist time, giving a total cost per patient of £70.
Cost of Alpha-Stim device - £450	
Proportion of patients using Alpha-Stim	
22% uptake of Alpha-Stim in patients who do not choose medication	The EAC model suggests that 15% of patients will choose medication over non-pharmacological treatments. In a cohort of 1000 patients, 22% of the remaining patients will choose Alpha-Stim. Published literature suggests 22% of patients will use Alpha-Stim.
Cost of individual CBT	

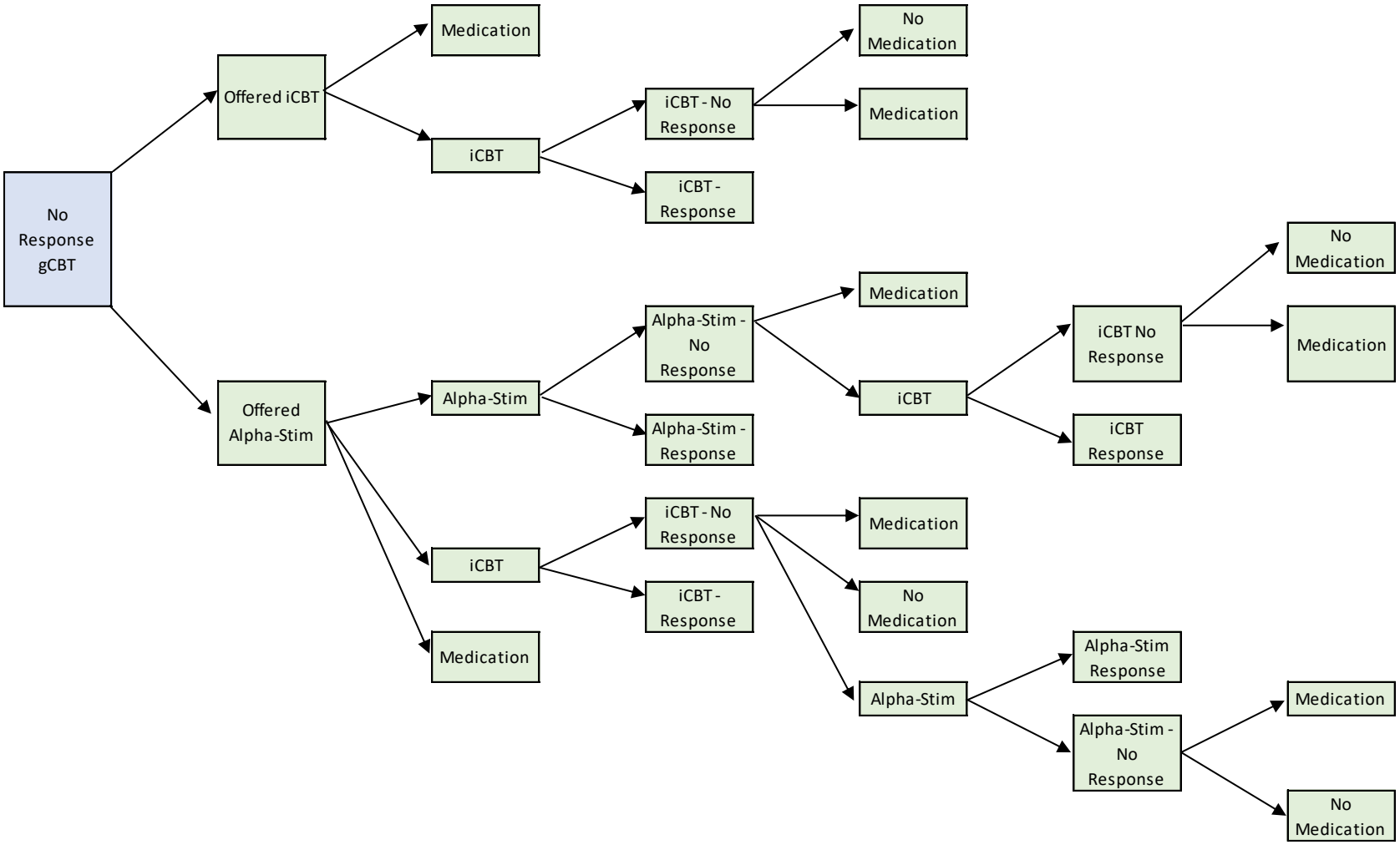
60 min iCBT session - £112.49 90 min iCBT session - £201.93	Cost reported in Radhakrishnan uplifted to 2017/2018 costs – still looking into whether there is a better way to cost this. 1 Cycle of Standard Practice iCBT is 8*60min sessions (£899.92 per cycle)
Model of iCBT	
Standard Practice (8*60min sessions) for a maximum of 1 cycles (number of sessions varied from 2 to 20)	Clinical experts suggest that there is no second cycle of iCBT but that the number of sessions per cycle can vary widely.

Appendix M: EAC Scenario 3: Assumptions, Decision Tree and Sensitivity Analysis

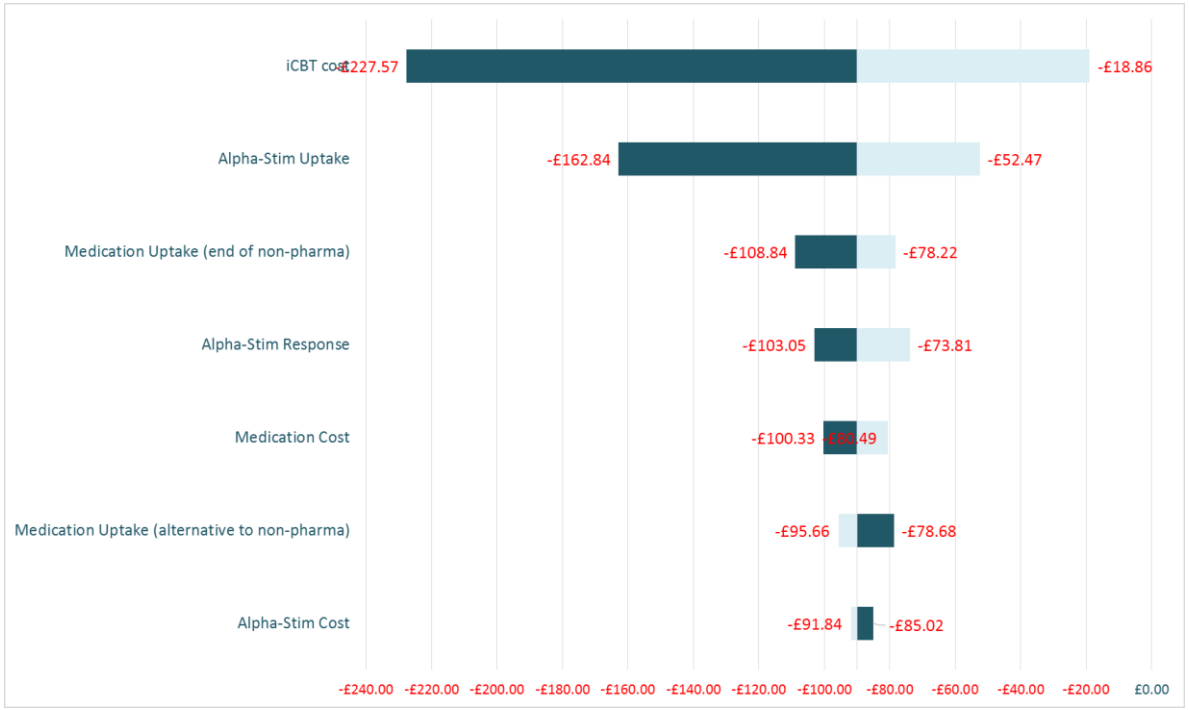
All assumptions for Scenario 3 are the same as those for the EAC base case with the exception that an additional branch has been added to the decision tree to reflect company feedback that a proportion of patients who initially choose iCBT but do not respond, will choose Alpha-Stim before medication.

Paramter	**Assumption**	**EAC Comment**
Patients in the Alpha-Stim arm choosing iCBT as initital treatment	15% of CBT non-responders will choose medication	The EAC accept that the order in which patients choose treatment options may vary with some patients who initially refuse Alpha-Stim in favour of iCBT may choose to try Alpha-Stim should they not respond to iCBT. The EAC recognise also that for patients who initially refused Alpha-Stim but did not respond to iCBT, not all of them will choose to revert to the option of Alpha-Stim as their reasons for refusal may not have changed.
	22% of remaining patients will chose Alpha-Stim (as in Morris et al)	
	Remaining patients end/move to next step	
	Alpha-Stim response rates remain the same	There is a possibility that the response to Alpha-Stim will be reduced following a non-response to iCBT however the EAC has not made any change.
	50% of non-responders to iCBT followed by Alpha-Stim will choose medication	The EAC consider it likely that there will be a cohort of patients who will choose not to have medication and instead move to the next step of the pathway.

EAC Scenario 3: Decision Tree



EAC Scenario 3: Tornado Diagram



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

MT477 Alpha-Stim AID for anxiety disorders

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 Cedar to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **28th July** 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.

23rd July 2020

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 14 lists items included with Alpha-Stim kit	We propose the wording be changed to “Alpha-Stim AID” kit.	Electromedical Products International, Inc. (EPI) manufacturers other Alpha-Stim models which have different accessories included in the kits. Specifying these are accessories included in the AID kit is more specific and accurate.	Thank you for your comment. The EAC has made the suggested change.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Current and frequency used in AID	• Page 25, 100 mA (milliamperes) should be 100 µA (microamperes) • Page 26, 0.05 Hz should be 0.5 Hz, and 500 uA should be 500 µA • µA or the term microamperes should be used throughout the document when referring to AID current.	Accuracy in description of current and frequency used in Alpha-Stim® AID	Thank you for your comment. The EAC has made the suggested changes throughout the report.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Treatment protocol	Proposed model for treatment is 60 minutes daily, which is consistent with research use of AID, where it is important that all variables be controlled. Actual clinical duration of each treatment is dependent upon tolerable current levels for each patient. Dosage is defined as current inversely proportional to time (i.e., the higher the current the quicker the treatment). Consistent with the Instructions for Use for Alpha-Stim AID, the patient should increase current slowly (500 µA is the highest setting) until a slight vertigo is experienced (a dizzy feeling, similar to the sensation of rocking on a boat), then decrease immediately until the dizziness stops. 20 minutes is enough time for most people if the current is set to at least 250 µA. 40 minutes to 1 hour is recommended if the current is at or below 200 µA.	Accuracy in potential NHS guidelines for treatment.	Thank you for your comment. The EAC has added in the suggested information for clarity in section 3 of the EAC report.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 8 states there is no evidence linking Alpha-Stim directly to drug treatment.	Lu & Hu (2014) compared participants treated with paroxetine only to participants treated with a combination of Alpha-Stim and paroxetine. The results of this study indicate Alpha-Stim can augment the effectiveness of paroxetine.	While some patients may opt for Alpha-Stim as the sole method of treatment, it is likely others will, if given the choice, utilize Alpha-Stim in conjunction with medication or therapy.	Thank you for your comment. The EAC has removed the statement in the executive summary which states that this is no evidence comparing Alpha-Stim directly to drug treatment, and added the following text: “One RCT showed improved anxiety symptoms in patients treated with Alpha-Stim and the drug paroxetine compared to paroxetine alone”

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 60, Figure 4, Decision Tree	Can Alpha-Stim be added as a third option with “Medication” or “No Medication” after “iCBT No Response.”	If a patient initially turned down Alpha-Stim in favour of iCBT, but does not respond to iCBT, the patient may be willing to try Alpha-Stim at that point.	Thank you for your comment. The EAC has amended the report to include an additional scenario (Section 9.2, section 9.3 (table 10) and Appendix M) whereby the possibility of patients who initially refused Alpha-Stim were willing to try it before moving to medication.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Randomization description on page 33 for Barclay & Barclay (2014).	The study was a true double-blind RCT. When the research devices are programmed for active and sham conditions for an RCT by EPI (the manufacturer), they are placed in the shipping container randomly. Investigators distribute devices to participants with no knowledge of which devices are active and which are sham. This protocol ensures double-blinding integrity, as neither investigator nor participants knows the condition of the device.	Whether this study was a truly randomized study is mentioned as a concern in this report. Standard EPI device preparation procedures for a double-blind study ensure randomization and blinding of both researchers and participants.	Thank you for your comment. The EAC has removed the statement in table 1 which states that the study may not be a true RCT. The EAC has also added the information provided by the company to section 5.2 of the report which clarifies some aspects of the methodology.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Standard of 24 months for determining long-term effectiveness of Alpha-Stim	No current method of mental health treatment, including CBT or medication, has guaranteed effectiveness for two years post treatment. In order for full effectiveness of medication, for example, the patient must continue with compliance in taking the medications.	Based on 39 years of real-world use with patients treating anxiety using Alpha-Stim, the cumulative effectiveness of this technology is known, and demonstrated in Morriss et al. (2019). Patients experience benefits from Alpha-Stim treatment for some time after discontinuing, but most chronic patients continue to utilize Alpha-Stim on a reduced schedule or PRN	Thank you for your comment. The EAC has included the research recommendation from NICE CG113 which states that ideally a study of sertraline vs CBT should have a 2 year follow-up. The EAC has moved this information to the section 12 on research implications section of the report. The executive summary has been changed to include the following statement: “The long-term benefit is

		to treat their anxiety before it elevates to clinically relevant severity.	unclear as only one study followed up patients for more than 6 weeks; this non-comparative study showed anxiety symptom improvements were sustained at 24 weeks." Section 8 has been amended to say "There is limited evidence on whether the effect of Alpha-Stim is maintained in the long term" instead of "no evidence".

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
MAUDE Report MW5025466 on page 45	We do not dispute the accuracy of this claim. Rather, we wish to advise the earclips have been redesigned since this incident to minimize the chance of this effect.	EPI has continuously improved the design of the earclip electrodes to ameliorate the occurrence of skin irritation and electrode burns. The most recent revision eliminated the last metal part in contact with skin by placing a plastic cap over the poles that are used to keep the felt electrodes in place. That seems to have reduced, if not eliminated skin irritation at the electrode site.	The EAC has added the following text to section 6 of the report: "The company has stated that since this incident the earclips have been redesigned to minimize the risk of this effect."

NICE National Institute for Health and Care Excellence

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Exclusion of Voris (1995) from clinical evidence	Reconsider exclusion of Voris (1995) as clinical evidence in this review.	According to page 28 of the EAC report, Voris (1995) is a triple-blind randomized study that drew "from a general psychiatric population suffering from a clinically significant anxiety dysfunction (incl. agoraphobia, GAD, panic attacks, OCD, social phobia, simple phobia)." (p. 28 of EAC report). As described in the unpublished article provided by EPI, the participants were randomized by seating choice prior to entering the treatment room to participate in the study. Chairs were assigned as either "control" (no treatment), "sham" (inactive treatment device), or "treatment" (active device), and participants self-selected their seats upon entering the room. In order to be diagnosed with an anxiety disorder, a patient must exhibit "clinically significant anxiety dysfunction." Therefore, the patients drawn from this psychiatric population with clinically significant anxiety dysfunction meet criteria for one of the anxiety disorders specified on pages 12 and 13 of this report. It should be noted that, on page 11, the population scope is defined as "people with anxiety disorders." Additionally, the inclusion criteria for this study was a STAI score between 40-70, which is consistent with recommended cut scores for the STAI to detect clinically significant anxiety. Therefore, Voris (1995) meets the population scope for clinical evidence. Results from this study indicate Alpha-Stim is effective at significantly reducing anxiety within a single 20-minute session.	Thank you for your comment. The EAC has carefully considered whether this study should be included as key evidence. The EAC has concluded that the study is relevant to the decision problem because the patients are a psychiatric population suffering from clinically significant anxiety. The EAC has included this unpublished RCT in the key evidence for this assessment report. Relevant changes have been made throughout the report.

		The study was unpublished only because Dr. Voris died before he could submit the article for publication. Ref: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879951/	

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Exclusion of Gibson & O'Hair (1987) from the clinical evidence.	Reconsider exclusion of Gibson & O'Hair (1987) as clinical evidence in this review.	The inclusion criteria of a score of 50 or more on the STAI (a measure identified in this report as a validated measure of anxiety) meets recommended cut off scores at the time of the study for a diagnosis of an anxiety disorder. Thus, even if a formal diagnosis is not provided for participants, the inclusion criteria utilized indicates they are experiencing clinically significant anxiety, which is the definition of an anxiety disorder. Therefore, the population in this study do fall within the scope of the population for this review. Results from this study indicate Alpha-Stim is effective at significantly reducing anxiety within a single 20-minute session. Especially when considered in conjunction with Voris (1995), it supports EPI's claims that most patients experience a benefit from the first treatment.	Thank you for your comment. The EAC has carefully considered whether this study should be included as key evidence. The EAC has concluded that the study is not relevant to the decision problem set out by NICE. The reason is that the participants in the study had not been diagnosed with an anxiety disorder (they were volunteers who responded to a newspaper advert). The EAC considers that the results of the study may be of interest to the committee and have presented key findings in table 5.

MT477 Alpha-Stim AID for anxiety disorders

Assessment Report Addendum

Produced by: Cedar

Authors: Judith White, Andrew Cleves, Susan O'Connell

Date completed: 14th August 2020

This Addendum has been produced in response to a request by NICE to review additional information provided by the company after submission of the assessment report. The following information relates to the Alpha-Stim AID Cranial Electrotherapy Stimulation (CES) Device

Preliminary and unpublished results from Royal et al. (2020, unpublished)

The company submitted an unpublished report of preliminary results from the Royal et al. (2020 unpublished)[1] study which was referenced in the original company submission. On page 51-52 of the assessment report, the EAC note that Royal et al. is an ongoing study, likely to be the study with trial number ISRCTN74799543. The company also provided the study protocol.

The methodology, results and the EACs critique of the unpublished report are presented in table 1 below. The information in these tables has been taken primarily from the unpublished report but supplemented by the study protocol where necessary.

Table 1 Methodology, results and critique of Royal et al. (2020)

Study name and location	**Study name:** Royal et al. (2020) UNPUBLISHED **Country:** UK **Sample size:** n=[redacted] treated with Alpha-Stim, n=[redacted] control
Design and intervention(s)	**Design:** Open-label, non-randomised study with retrospective control group. **Intervention:** Nurse-led primary care mental health clinic for young people; Alpha-Stim AID incorporated into a new pathway with i-spero smartphone application and used either alone or in combination with other treatments. Duration of treatment was 6 to 10 weeks; frequency and duration of daily use was not reported. The i-spero app was used to plan and monitor response to therapy. **Control:** Usual care (did not enter new pathway) and were seen by a doctor in the first instance. The authors state that control group scores were collected over same period as intervention group and came from patients with new presentations of minor mental health problems which would have been suitable for the pathway had space been available.
Participants and setting	**Participants:** Adult patients attending the participating practice requesting an appointment to discuss a mental health problem. The author has

[1] Royal S, Keeling S, Kelsall N (2020) An evaluation of the cost-effectiveness of a new technology (Alpha-Stim) to treat mild to moderate anxiety in young people attending a nurse-led primary care clinic. Unpublished report communicated to NICE.

	communicated the following information: "This was a primary care trial and the only inclusion criteria were that participants were registered with the practice and rang (or presented at reception pre-covid) requesting an appointment to discuss a mental health problem. The only exclusion criteria were acute suicidal ideation and acute intoxication. All of those in the study had either an anxiety disorder or mixed anxiety and depression diagnosed at assessment with the clinician. Alpha-stim treatment was only offered to those with a significant element of anxiety in their symptomatology." **Setting:** Single GP surgery in Nottingham, UK
Outcomes and follow-up	GAD-7 score collected at baseline and then after treatment (6-10 weeks), collected using the i-spero app.
Results	[redacted] in anxiety scores in the intervention and control groups. [redacted] was made between the groups. Intervention: Baseline GAD-7 score was [redacted], after treatment was [redacted] ([redacted]). Control: Baseline GAD-7 was [redacted], after treatment was [redacted] ([redacted]) No adverse events were reported. [redacted] broke an Alpha-Stim device but returned study data. [redacted] patients (denominator not reported) expressed a high degree of satisfaction with the Alpha-Stim treatment. [redacted] negative feedback was received. Number of contacts: [redacted] contacts over [redacted] days of supervised management (contact every [redacted] days) in the intervention group; [redacted] contacts in [redacted] days (contact every [redacted]) days in the control group. *In the discussion section, the authors surmise that* [redacted].
EAC comments	• Pragmatic design in an NHS setting means this study is of relevance to the decision problem, however the parallel use of the i-spero app alongside Alpha-stim is of more limited generalisability to the current patient pathway. • Open label, at risk of bias as patients assess their own symptoms. • No sample size calculation. • Eligibility criteria not reported (although obtained from protocol). • Study sample is young adults recruited at a University health centre, [redacted] female. Applicability of results may be limited to other groups. • Validated outcome measure used (GAD-7) although collected used an app called i-spero. Method for obtaining feedback on the device not described. • Variable intervention duration and frequency of use not described. Time point for follow-up variable and not clearly described (the report says that scores were collected after 6 to 10 weeks of treatment).

	• Alpha-Stim used alongside other non-study interventions which were not described. Treatments in control arm not described. • Limited demographic data presented for both intervention and control groups. • Retrospective control group identified from review of medical notes; not matched with intervention group. • Number of participants invited to participate not reported. • [redacted] cost data reported in preliminary results. • Devices loaned to clinic by company.

Conclusion

The EAC concludes that the unpublished study provides some additional clinical evidence to suggest that Alpha-Stim can be used to treat anxiety however there are some concerns regarding the applicability and generalisability of the study at this time. The study is a non-randomised 'before and after study' in which Alpha-stim was introduced and used alongside other interventions which were not described. Comparison patients were drawn from retrospective review of medical records. Patients were required to complete the GAD score via a smartphone app, which itself is reported to be a new technology, and [redacted]. The EAC concludes there is a [redacted] risk of bias based on the currently available information of the study methodology. Only young people, primarily [redacted] were recruited to the study which may limit the generalisability of the results to the wider NHS population although the EAC acknowledges that [redacted] (see Assessment Report; Special Considerations).

[redacted] cost details were reported in the preliminary results and it is therefore [redacted] on whether the use of Alpha-Stim in this setting would be [redacted]. While the EAC acknowledges and agrees that [redacted] The EAC considers that there is a need to fully understand the primary care pathway and all the associated costs before a meaningful economic model could be produced. In addition, based on this study there are possible additional costs associated with the use of the I-spero app which would need to be considered.

The EAC concludes that the addition of this study data does not change the overall conclusions as stated in the Assessment Report (section 10) – Alpha-Stim appears to be both a clinically effective and cost saving approach to treating anxiety disorders.

EAC response to company's claimed benefits

Benefit claimed by company	Available evidence	EAC comment
Patient benefits		
Reduction in anxiety symptoms	All included studies report a reduction in anxiety symptoms following Alpha-Stim treatment (2 published RCTs, 3 published non-comparative studies, and 2 unpublished reports).	Agree, based on weak evidence.
Reduced reliance on medications	None	No evidence to support this claim
System benefits		
Reduced need for Cognitive-Behavioural Therapy (CBT)	Supported by published cost model (same as de novo model in company submission) and in cost models amended by EAC.	Agree (extent of cost saving may be lower than presented by company, possibility of cost neutral)
Improved treatment in subgroups where additional medication is contraindicated	None (addition of Alpha-Stim provides alternative treatment, no evidence that it would improve treatment in subgroups)	No evidence to support this claim
Cost benefits		
Reduced cost for treatment of anxiety compared to current pathway.	Supported by published cost model (same as de novo model in company submission) and in cost models amended by EAC.	Agree (based on assumptions around uptake and costs of other treatments)
Sustainability benefits		
Patients can re-use Alpha-Stim devices in their homes.	Patients use device at home but return it to NHS provider after 6-12 weeks of treatment.	Unclear

MT477 Alpha-Stim AID for anxiety disorders

Assessment Report Addendum

Produced by: Cedar

Authors: Susan O'Connell, Andrew Cleves, Judith White

Date completed: 09/09/2020

This Addendum has been produced in response to a request by NICE to review additional information relating to response rates for treatment with Alpha-Stim and iCBT used in the economic analysis.

The following information relates to the Alpha-Stim AID Cranial Electrotherapy Stimulation (CES) Device.

Background

In the company submission and EAC base case, Alpha-Stim is cost saving in all scenarios tested. Discussion with an IAPT expert has suggested that the response rates used in the analysis may be contributing to an over-estimation of the effectiveness of Alpha-Stim leading it to be a dominant treatment in all instances.

In the Assessment Report an assumption is made that the response rate to Alpha-Stim is 47.2% (a value derived from the Morriss et al. 2019 study) and that for patients who do not respond to Alpha-Stim and go on to individual CBT (iCBT), the response rate to iCBT is 54.2% (from Gyani et al. 2013). This gives a cumulative response rate of 73%. While this response rate may be a fair assumption, there is evidence from Morriss et al. (2019) which suggests that response rates for patients treated with Alpha-Stim might differ depending on whether they a) receive iCBT at any point, b) the amount and timing of iCBT received and c) whether they completed the recommended course of Alpha-Stim. In addition, the Alpha-Stim response rate of 47.2% from Morriss et al. (2019) is based on all patients treated with Alpha-Stim, some of whom may have also undergone iCBT during the study and therefore may be confounded by the impact of any iCBT.

One clinical expert suggests that Alpha-Stim and iCBT work in different ways; Alpha-Stim calms the mentation (worrying) and physiological arousal while iCBT gives the person cognitive and behavioural strategies to utilise, particularly when there are exacerbations of anxiety. They may therefore be complementary treatments and additive treatment effect is plausible.

Although the economic analysis in the Assessment Report included a sensitivity analysis around the possible response rates, this may not have captured the full extent of the possible response rates and their impact on the costs. The EAC has therefore carried out further analysis to investigate the impact of changing response rates on the cost savings.

Response Rates

Currently Alpha-Stim is positioned as a treatment option in the IAPT service to be offered to patients who are on the waiting list for iCBT; patients can choose to try Alpha-Stim or wait for iCBT. If a patients chooses to try Alpha-Stim they remain on the waiting list for iCBT and there is a possibility that they will start iCBT while still using Alpha-Stim. This may mean that patients stop Alpha-Stim when they start iCBT or they may carry on with both treatments. Conversely, depending on waiting list times, there is a chance that patients who complete Alpha-Stim or who stop Alpha-Stim because they are not responding will have to wait for iCBT leading to a gap in treatment. All of these scenarios might conceivably have an impact on the potential response rate to treatment which will have an impact on the cost savings.

Results from one study (Morriss et al, 2019) suggest that response rates may vary from as low as 12.7% to as high as 68% depending on the treatment combination and timing (table 1) however as the current studies have not been designed to investigate combination treatment and response rates for some of these treatment combinations have been based on small patient numbers, they should be considered with some caution and discussion. No other studies report response rates for combination treatments in sufficient detail to populate the cost model.

Table 1: Alpha-Stim Response Rates based on data from Morriss et al (2019)

	N	Response	Source

All patients	161	77	47.8%	Morriss et al (2019)
A/S only	81	53	65.4%	Morriss et al (2019)
A/S + Any CBT	80	24	30%	Morriss et al (2019)
A/S+CBT completed within the same 12 week period	25	17	68%	Morriss et al (2019)
Stopped or completed alpha stim and then had iCBT	55	7	12.7%	Morriss et al (2019)

Cost of Alpha-Stim

The current cost of Alpha-Stim in the model is £70 per patient based on information provided by the company and is costed on the basis of the number of patients using a device plus some additional costs for consumables and therapist time.

The decision on how Alpha-Stim is used in the clinical pathway is likely to have some impact on the any cost savings. The cost of providing Alpha-Stim is likely to differ depending who provides the device to the patient and how much patient contact time is required. The EAC has provided some alternative costs for Alpha-Stim using different staff costs PSSRU (Curtis and Burns 2019) (table 2) but has not explored the impact of the higher costs associated with nurse time as it is assumed that this would form part of the primary care pathway.

Table 2: Alpha-Stim Costs

Company Submission	EAC Base Case	Alternative Costs
£70 per patient	£70 per patient (in sensitivity analysis £56 to £84 per patient)	£84 to £124 per patient
• Training cost over lifetime of device (£5) • Other costs per year and over lifetime of device (£25) • Cost per patient i.e. £450 purchase cost / 15 patients (£30) • Consumables per patient (£10)	As per company costs	Band 4 (e.g. HCSW) : • Cost per hour of patient-related work (£44) • Cost per patient i.e. £450 purchase cost / 15 patients (£30) • Consumables per patient (£10) Total: £84 Band 5 (qualified nurse): • Cost per hour of patient-related work (£60) • Cost per patient i.e. £450 purchase cost / 15 patients (£30) • Consumables per patient (£10) Total: £100 Band 6 (qualified nurse) • Cost per hour of patient-related work (£84) • Cost per patient i.e. £450 purchase cost / 15 patients (£30) • Consumables per patient (£10)

		Total: £124

Cost of iCBT

In the EAC Assessment Report the cost of individual CBT is costed at £112.49 per 1 hour session and a course of iCBT is assumed to comprise 8 sessions for a total cost of £899.92. This is based on published data (Radhakrishnan et al, 2013) and was calculated based on total spend information submitted by 5 primary care trusts in the East of England in the 2009/10 financial year.

A second publication (Mavranezouli et al, 2020) costed trauma-focused CBT at £101.33 per 1 hour session based on the hourly cost of direct patient contact for a band 7 psychological therapist or £42 per 1 hour session based on the hourly cost of direct patient contact for a band 5 Psychological Well-being Practitioner (PWP). The EAC has therefore investigated the impact of the lower cost of iCBT delivered by a band 5 PWP.

Table 3: iCBT Costs (8 one hour sessions)

	Cost of iCBT		
	Company Submission	EAC Base Case	Alternative Cost
Base Case (8 x 1 hour sessions)	£899.92 per patient	£899.92 per patient	£338.64 (band 5)
Low Cost (2 x 1 hour sessions)	N/A	£224.98	£84.66
High Cost (20 x 1 hour sessions)	N/A	£2,249.80	£846.60

Results

The key assumptions in the additional analysis are as follows (table 4):

- In a cohort of 1,000 patients, 15% of patients will choose medication as their first treatment
- All remaining eligible patients in the cohort choose Alpha-Stim
- Cost of Alpha-Stim is £70 per patient. This cost is the same whether a patient completes a course of Alpha-Stim or not.
- Cost of iCBT is £112.49 per 1 hour session with a total cost for iCBT of £899.92 based on the assumption that a course of iCBT comprises 8 sessions.

- No change is made to the cost of iCBT treatment alone as this is explored in the Assessment Report.
- Cost of Alpha-Stim+iCBT assumes the full cost of Alpha-Stim (£70) plus the full cost of iCBT (£899.92) for a total cost of £969.92. A low cost of Alpha-Stim + iCBT assumes the cost of Alpha-Stim plus 2 sessions of iCBT and high cost comprising the cost of Alpha-Stim plus 20 sessions of iCBT. This change is made only for combination treatment costs.
- Response rates for iCBT is 54.2% as reported in published literature (Gyani et al, 2013).
- Response rates for treatment involving Alpha-Sim vary depending on the treatment combination (see table 1 for details).

Table 4: Parameters in the Model

Parameter	Value	Comment
Cost of Alpha-Stim	£70	Calculated based on information provided by the company
Cost of iCBT	£899.92	Based on a cost of £112.49 per 1 hour session with a total of 8 sessions per treatment.
Cost of Alpha-Stim + iCBT	£969.92	Based on the full cost of Alpha-Stim plus the cost of a full course of iCBT.
Response Rate – iCBT Alone	54.2%	As in published literature (Gyani et al, 2013)
Response Rate – Alpha-Stim Alone	65.4%	As in published literature (Morriss et al, 2019). Full details in table 1.
Response Rate: Alpha-Stim + Any CBT	30%	As in published literature (Morriss et al, 2019). Full details in table 1.
Response Rate: Alpha-Stim+CBT completed within the same 12 week period	68%	As in published literature (Morriss et al, 2019). Full details in table 1.
Response Rate: Stopped or completed Alpha-Stim and then had iCBT	12.7%	As in published literature (Morriss et al, 2019). Full details in table 1.

The company submission calculated that Alpha-Stim is cost saving compared with iCBT (-£540.88) and the EAC base case calculated a cost saving with Alpha-Stim of -£80.79 when considering a 22% uptake and -£367.22 when all patients chose to use Alpha-Stim (See EAC Assessment Report, Section 8 for full details).

Further analysis presented in this addendum to investigate the potential impact of different response rates (table 2) suggest that when patients are treated with combinations of Alpha-Stim and iCBT, the impact on the cost savings is significant, as follows.

Alpha-Stim Alone versus iCBT Alone

Patients who use Alpha-Stim alone had a response rate of 65.4% (Morriss et al, 2019). Using this response rate, Alpha-Stim alone is cost saving compared with iCBT alone (-£446.82).

Alpha-Stim plus iCBT within the same 12 week period versus iCBT Alone

The response rate (68%) following Alpha-Stim plus iCBT within the same 12 week period is higher however the cost of the additional iCBT means that Alpha-Stim + iCBT is cost incurring compared with iCBT alone (£52.04) based on a cost of Alpha-Stim plus 8 sessions of iCBT. When reducing the number of iCBT sessions to 2, the treatment is cost saving compared with Alpha-Stim alone (-£521.66) and increasing the number of iCBT sessions to 20 makes the treatment cost incurring compared with iCBT alone (£1199.44).

Alpha-Stim plus any iCBT versus iCBT Alone

The response rate for patients who had Alpha-Stim plus any iCBT was 30% (Morriss et al, 2019). Using this response rate results in this treatment combination being cost incurring compared with iCBT alone (£72.59) however this is based on a cost of Alpha-Stim plus 8 sessions of iCBT. It is not known how many sessions of iCBT patients in this group underwent, so varying the cost of the Alpha-Stim + iCBT (all other parameters remain the same) results in a range from -£501.11 cost saving (Alpha-Stim + 2 iCBT sessions) to £1,219.98 cost incurring (Alpha-Stim plus 20 sessions iCBT) compared with iCBT alone.

Alpha-Stim followed by any iCBT versus iCBT Alone

A small number of patients started Alpha-Stim treatment and then followed on with iCBT. The response rate for this group was 12.7%. Using this response rate, Alpha-Stim followed by iCBT is cost incurring compared with iCBT alone (£81.94) however

as again it is not known how many sessions of iCBT these patients underwent, the results range from -£491.76 cost saving to £1,229.34 cost incurring compared with iCBT alone.

Table 4: Comparison of cost-savings based on different response rates for different treatment combinations

Treatment	Cost per patient	Alpha-Stim Cost Savings	High*	Low*
iCBT Only	£808.70	N/A	N/A	N/A
EAC BASE CASE – All patients choose Alpha-Stim (73% Response Rate)	£441.57	-£367.22	N/A	N/A
Alpha-Stim Only (65.4% Response Rate)	£361.96	-£446.82	N/A	N/A
Alpha-Stim + iCBT within 12 weeks (68% Response Rate)	£860.82	£52.04	-£521.66	£1,199.44
Alpha-Stim + Any iCBT (30% Response Rate)	£881.37	£72.59	-£501.11	£1,219.98
Alpha-Stim Followed by iCBT (12.7% Response Rate)	£890.73	£81.94	-£491.76	£1,229.34

*Low cost savings are based on assumption that patients in the iCBT arm complete full iCBT (8 sessions) but patients in combination arm complete 20 sessions which increases the cost for combination Alpha-Stim + iCBT treatment. High cost saving based on assumption that patients in combination arm complete 2 sessions of iCBT.

Reduced Cost of iCBT

Considering the alternative, lower cost of iCBT delivered by a band 5 PWP, in the EAC base case the cost per patient for iCBT is reduced to £331.70 and the cost of Alpha-Stim reduces to £227.45 per patient. The Alpha-Stim cost saving is reduced to -£104.25 per patient (range -£342.23 to £14.25 based on a cost for 2 iCBT sessions and a cost for 20 iCBT sessions).

Considering Alpha-Stim alone with a response rate of 65.4% and a reduced cost of iCBT, Alpha-stim remains cost saving compared with iCBT alone but the cost saving is reduced to -£134.81 (-£566.57 to £81.08 based on a cost for 2 iCBT sessions and a cost for 20 iCBT sessions).

For combination treatments, the assumption is that the patients in the iCBT branch will complete a full course of 8 sessions of iCBT incurring the full cost of iCBT whereas in the combination treatment arms, patients will complete varying numbers

of iCBT sessions and may or may not complete their course of Alpha-Stim. The cost of Alpha-Stim is the same regardless of a completed course of treatment but the cost of iCBT will increase or decrease depending on the number of sessions. The cost of combination treatment is therefore reduced to £154.66 (Alpha-Stim plus 2 iCBT sessions) to calculate the high value and increased to £916.60 (Alpha-Stim plus 20 iCBT sessions) to calculate the low value for each treatment combination.

Table 5: Cost Savings using lower cost of iCBT (£42.33 per hour)

Treatment	Cost per patient	Alpha-Stim Cost Savings	High	Low
iCBT Only	£331.70			
EAC BASE CASE – All patients choose Alpha-Stim with non-responders going on to complete a full course of iCBT (73% Response Rate)	£227.45	-£104.25	-£342.23[1]	£14.75[1]
Alpha-Stim Only (65.4% Response Rate)	£196.89	-£134.81	-£566.57[1]	£81.08[1]
Alpha-Stim + iCBT within 12 weeks (68% Response Rate)	£383.73	£52.03	-£565.05[2]	£82.60[2]
Alpha-Stim + Any iCBT (30% Response Rate)	£404.28	£72.58	-£544.50[2]	£103.15[2]
Alpha-Stim Followed by iCBT (12.7% Response Rate)	£413.64	£81.94	-£535.14[2]	£112.51[2]

[1]High value is based on patients only having 2 sessions of iCBT, low value based on patients having 20 sessions of iCBT (change made to both iCBT and Alpha-Stim branches).

[2] Low cost savings are based on assumption that patients in the iCBT arm complete full iCBT (8 sessions) but patients in combination arm complete 20 sessions which increases the cost for combination Alpha-Stim + iCBT treatment. High cost saving based on assumption that patients in combination arm complete 2 sessions of iCBT (changes made only to Alpha-Stim branch).

Conclusions

Alpha-Stim alone is cost-saving compared with iCBT alone. Combination treatment (Alpha-Stim plus iCBT) may be cost saving compared with iCBT alone however this depends on the response rates. From the results of one study (Morriss et al. 2019), Alpha-Stim and iCBT treatment completed within the same 12 week period has a higher response rate than either iCBT alone or Alpha-Stim alone however the increased cost of providing both treatments results in Alpha-Stim+iCBT becoming cost incurring compared with iCBT alone. In addition, some combinations of Alpha-Stim plus iCBT may have reduced response rates compared with Alpha-Stim alone

or iCBT alone and a lower response rate in addition to the increased cost of Alpha-Stim plus iCBT reduces the potential for cost saving.

The EAC conclude that based on the current evidence, Alpha-Stim alone is cost saving compared with iCBT alone. When considering combination treatment of Alpha-Stim plus iCBT however the results are cost incurring in all combination scenarios compared with iCBT alone.

Key Points for Consideration

The EAC consider the following points should be considered for discussion

- Morriss et al (2019) was not designed to compare response rates in different treatment combinations,
- No details are available for the number of iCBT sessions patients completed,
- No details are available for the proportion of patients who did not complete Alpha-Stim once they started iCBT,
- Cost of providing iCBT will vary depending on how many sessions a patient undergoes and who delivers the sessions,
- Cost of Alpha-Stim may be higher if access is through a GP practice nurse

Erratum

In the company submission and in the EAC base case the response rate for Alpha-Stim was included as 47.2% however the actual response rate should be 47.8%. This small error has been systematically introduced due to an inconsistency in the published paper (Morriss et al 2019) and does not substantially alter the results. For completeness, the EAC presented all the results using 47.2% and updated to 47.8% (table 6).

Table 6: Corrected costs

	Alpha-Stim Response Rate – 47.2%	Alpha-Stim Response Rate – 47.8%
Company Model	-£540.88	-£548.64
Adjusted Company Model	-£120.85	-£122.58
EAC Base Case (22% Alpha-Stim uptake)	-£80.79	-£81.70
Scenario 1 (All patients choose Alpha-Stim)	-£367.22	-£371.34
Scenario 2 (lower iCBT response to 2nd cycle)	-£97.25	-£98.74
Scenario 3 (Alpha-Stim as an option following iCBT)	-£88.43	-£89.36

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Alpha-Stim AID for anxiety disorders

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

1 The technology

Alpha-Stim AID (Electromedical Products International, Inc) is an electrotherapy device for managing anxiety, insomnia and depression. This guidance focuses on the use of Alpha-Stim AID for anxiety disorders. The technology was developed in 1981 in the US, and Alpha-Stim AID is the latest model.

Alpha-Stim AID uses cranial electrotherapy stimulation (CES), by providing a variable electrical microcurrent to the brain which stimulates alpha wave electrical activity. The current has a pulse repetition rate of 0.5 hertz and is composed of bipolar asymmetric rectangular waves in a cycle that repeat periodically at 10 second intervals.

Alpha-Stim AID is the size of a mobile phone and has a pair of small clips with removable soft pads that need to be moistened with a solution which conducts electricity. The current is applied by these clips that attach to the ear lobes and the strength of the current can be adjusted. Alpha-Stim AID is recommended to be used for between 20 and 60 minutes every day, every other day, or on an as-needed basis. Alpha-Stim AID is battery powered and portable and can be self-administered at home, or by a healthcare professional in a hospital or clinic setting.

Alpha-Stim AID is not suitable for people with cardiac pacemakers and implanted defibrillators. The technology may be suitable for use during pregnancy. Children should use Alpha-Stim AID under adult supervision.

2 Proposed use of the technology

2.1 Disease or condition

Anxiety disorders are common mental health conditions and include generalised anxiety disorder and social anxiety disorder. There is considerable variation in the severity of anxiety disorders, and some are associated with significant long-term disability. They can be distressing for the person affected, their families, friends and carers, and can have an impact on

their local communities. Anxiety disorders can have a lifelong course of relapse and remission.

2.2 Patient group

In the UK in 2010, 8.2 million adults were diagnosed with an anxiety disorder and the cost of treatment for the anxiety disorder was estimated to be £11,687 for each adult, and it is one of the most costly psychiatric and neurological disorders (Fineberg et al. 2013). An adult psychiatric morbidity survey in England reported that the 1-week prevalence of generalised anxiety disorder was 6.6% and anxiety disorders were more common in women than in men, with the most apparent difference in those aged between 16 and 24 (respectively GAD 9.0%; phobias 5.4%; OCD 2.4%; and panic disorder 2.2%) than in other age sex groups (McManus et al. 2014).

2.3 Current management

NICE's guideline on generalised anxiety disorder and panic disorder in adults provides principles of care for people with generalised anxiety disorder (GAD). It also recommends a stepped-care model to organise service provision and to help people with GAD, their families, carers and practitioners to choose the most effective intervention. The stepped-care model is described in the assessment report (page 19).

Improving Access to Psychological Therapies (IAPT) services provide evidence-based psychological therapies to people with anxiety disorders and depression. According to one expert, IAPT teams are the standard structure of service provision for people with anxiety and depression in most regions of England. IAPT teams deliver the NICE-recommended stepped-care model for GAD.

NICE's guideline on social anxiety disorder: recognition, assessment and treatment provides treatment principles for treating adults with social anxiety disorder. It recommends that individual cognitive behavioural therapy (CBT) that has been specifically developed should be offered to adults with social anxiety disorder. If the person wishes to proceed with a pharmacological intervention, a selective serotonin reuptake inhibitor (SSRI) (escitalopram or

sertraline) should be offered. For adults who decline cognitive behavioural and pharmacological interventions, short-term psychodynamic psychotherapy that has been specifically developed to treat social anxiety disorder should be considered. The guideline also provides recommendations on interventions for children and young people with social anxiety disorder. Pharmacological interventions should not be offered to treat social anxiety disorder in children and young people.

2.4 Proposed management with new technology

Alpha-Stim AID is intended to be used for the treatment of anxiety disorder, either as a stand-alone or an add-on treatment. The company have proposed 3 clinical pathways where the technology could be used to treat people with generalised anxiety disorders:

- Primary care GP services
- Primary care Improving Access to Psychological Treatment (IAPT)
- Secondary care mental health or long-term conditions pathway.

The two primary care pathways relate to a patient presenting to a GP setting or self-referring to an IAPT service, and then being diagnosed with GAD. Alpha Stim would be offered to patients as a treatment instead of drugs or high intensity psychological interventions after steps 1 (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective. Also, patients often have to join a waiting list for high intensity psychological interventions (individual cognitive behaviour therapy (iCBT)) and Alpha-Stim may also be a treatment option for patients whilst they wait for this intervention. The EAC have provided further information about the GAD clinical pathway (see page 16 of the assessment report).

In the secondary care setting, an existing patient with serious mental illness or long-term physical condition diagnosed with comorbid GAD would follow the GAD clinical pathway and could be offered Alpha-Stim at step 3. In some case additional medication may be undesirable e.g. sedation, addiction potential or contraindicated.

3 Company claimed benefits and the decision problem

The main claimed benefits and decision problem from the scope are attached as Appendix D).

The company has proposed a variation to the population in the decision problem. The rationale provided is that there is evidence available to support the use of the device in patients who have symptoms of anxiety as well as those with a diagnosis of anxiety. The EAC accept that the technology could be beneficial to a broader population who report anxiety symptoms or may be at risk of experiencing anxiety. However, after carefully considering the company claims related to those with anxiety, the EAC decided that the assessment should focus on those with a diagnosis of anxiety to best identify the benefits to patients and the NHS. Therefore, the EAC have not accepted this change to the scope.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company included 24 studies in the clinical evidence submission. The EAC conducted its own systematic search and identified 5 published studies and 1 unpublished study which are relevant to the decision problem. All except 1 study (Bystritsky et al. 2008) were included by the company. The rationale for the study selection is described in section 4.2 of the assessment report (page 22).

Details of the studies included by the EAC for the evidence base are summarised in Table 1 (see below). The 6 studies are 3 RCTs (2 published and 1 unpublished) and 3 non-comparative observational studies. The three RCTs used different comparators: Barclay & Barclay (2014) compared Alpha-Stim treatment against a sham device (identical to the active device, however the ear clip electrodes did not emit electricity). Voris (1995) compared Alpha-Stim AID with 2 control groups: a sham device and a no treatment group. Finally, Lu & Hu (2014) compared Alpha-Stim AID plus paroxetine (a selective

serotonin reuptake inhibitors drug used to treat anxiety disorders) with paroxetine alone. The EAC critically appraised the studies and found 2 of them were at high risk of bias (Barclay & Barclay 2014; Voris 1995) and the other had some concerns regarding the risk of bias (Lu & Hu, 2014) because of no published protocol or clinical trial database.

The EAC rated the 3 non-comparative observational studies as poor quality because of population selection bias (Morriss et al. 2019 and Overcash 1999), high loss to follow up and missing data (Morriss et al. 2019 and Bystrisjy et al. 2008).

Results from the studies included in the evidence base are presented in Table 4 of the assessment report (page 42). All studies reported anxiety symptom scores before and after treatment with Alpha-Stim AID, showing a statistically significant improvements in anxiety score during the study follow-ups, ranging from 5 to 24 weeks. Three RCTs also showed statistically greater improvements in anxiety scores comparing adults used Alpha-Stim AID with those in the control group (paroxetine, sham device, or no treatment). Table 6 in the assessment report (page 51) summarises the anxiety score results reported in the studies. Other outcomes reported in the included studies are:

- Quality of life was reported in 2 studies EQ-5D-5L scores improved significantly from baseline to the end of study follow-up (24 weeks) (Morriss et al. 2019). Lu & Hu (2014) used the WHOQOL-BREF tool and there was significant difference in the physical domain of QoL score between the intervention and control groups.

- Self-reported depression was reported in 3 studies (Barclay & Barclay, 2014; Bystritsky et al. 2008; Morriss et al. 2019), and results indicated a significant decrease in depression scores measured before and after using Alpha-Stim.

- Insomnia and functioning were reported in Morriss et al. (2019), indicating a significant reduction in insomnia score and a significant improvement in work and social functioning score before and after using Alpha-Stim AID.

- Severity of illness was reported in Lu & Hu (2014), showing a reduction in severity score in both intervention and control groups with a significant greater reduction in the intervention group than the control group.

The EAC also identified 7 studies (4 comparative and 3 non-comparative studies) reported potentially relevant data on the effect of Alpha-Stim AID on managing anxiety symptoms but study populations were out of the scope because they did not have a confirmed diagnosis of anxiety disorder. Results of the 4 comparative studies reported significantly reduced anxiety symptoms when treated with Alpha-Stim AID compared with the control group (see Table 5 of the assessment report, page 47). Two of the 3 non-comparative studies reported significant improvement in anxiety symptoms after treatment with Alpha-Stim AID (the third study did not carry out a statistical comparison).

The company presented a meta-analysis on the effect of Alpha-Stim AID on anxiety based on the results from 10 RCTs. The results are presented as academic-in-confidence. The EAC reviewed the meta-analysis and considered its results were not generalisable to a population with an anxiety disorder. The EAC did not undertake a meta-analysis of the evidence because of the limited evidence (only 3 studies) and heterogeneity in settings, interventions and outcome reported in the studies.

Despite weaknesses in the evidence base, the EAC considers that statistically significant improvements in anxiety symptoms were observed in participants treated with Alpha-Stim AID in the short term (6 weeks) but long-term benefits were only reported in one study. It suggests that Alpha-Stim AID could be considered as a treatment option for people with GAD who have not responded to low intensity psychological interventions such as individual non-facilitated self-help, individual guided self-help and psychoeducational groups. However, the EAC notes there is no evidence to support using Alpha-Stim AID as a replacement for high intensity psychological interventions or drugs. Also, there is no evidence on whether the effect of Alpha-Stim AID is equal across a range of baseline symptom severities.

The EAC also noted that social anxiety disorder is within the scope of this assessment. However, the company submission did not include any reference to the use of Alpha-Stim AID for the treatment of social anxiety disorder and there was no evidence to support its use for this condition.

Table 1 Summary of studies assessed by the EAC, reproduced from table 1 of the assessment report

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
Comparative studies				
Barclay & Barclay (2014) USA n=115	**Design:** Double blind, (randomised) controlled trial. **Intervention:** Alpha-Stim 100 (n=60). used daily for 1 hour for 5 weeks. Current intensity was pre-set and locked at 100 µA (subsensory level).. **Control:** Sham device (n=55) for 5 weeks. The sham CES devices were identical to the active device, except the ear clip electrodes did not emit electricity. **Funding:** Unfunded study that took place in private practice setting. No conflict of interest reported. **Status:** Published.	**Participants:** Adults with primary diagnosis of anxiety Comorbid depression allowed. **Setting:** USA (central Virginia), private primary care setting.	**Co-primary outcomes:** HAM-A (anxiety) and HAM-D_{17} (depression) questionnaires. Response to treatment was defined as a ≥50% reduction in HAM-A and HAM-D_{17} measures. **Secondary:** None. **Follow-up:** Measurements took place using the HAM-A and HAM-D_{17} at the end of weeks 1, 3, and 5.	Random allocation unclear. Company has provided further information on randomisation and blinding. Detail in paper, page 173 'The participants were randomized into 2 groups;. However, study record (NCT01533415) states non-randomised. Intention to treatment (ITT) analysis not used; for the intervention 5% and for the control 7% were lost to follow-up due to lack of compliance/study fidelity and not included in analysis. No information provided as to who conducted assessments. Not explicit if assessors blind. Clinically relevant change in score not described, rather Cohen's d effective size of 0.5 used in sample size calculation. The manufacturer supplied 20 devices for the study.
Lu & Hu (2014) China n=120	**Design:** Open label, randomised controlled trial. **Intervention:** Alpha-Stim SCS device for 6 weeks,	**Participants:** Adults with diagnosis of anxiety disorder and at least primary school education.	**Primary:** HAM-A reductive ratio was the indicator for efficacy evaluation. HAM-A reductive ratio ≥75% is clinically cured, 50% to74% obviously improved, 25% to	Open label, at risk of bias as patients assess their own symptoms. ITT analysis used (no loss to follow-up).

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
	daily for 60 continuous minutes, for a total of 42 treatments. At the initial visit the investigator set the sensory threshold for each participant. The intervention group was treated with paroxetine (10-20 mg/d) in combination with CES therapy (n=60). **Control:** Paroxetine (10-20 mg/d) (n=60) **Funding:** Not reported. **Status:** Published	**Setting:** Inpatient or outpatient departments of a mental health centre. Author affiliation is in China but setting not reported.	49% improved, and <25% ineffective. Significant efficacy rate = [(number of cured cases + number of obviously improved cases)/ total number]×100%. **Secondary:** CGI-SI was the secondary indicator for efficacy evaluation. WHO quality of life measurement. **Follow-up:** HAM-A was assessed in Weeks 0, 2, 4 and 6, and CGI-SI and WHOQOL-BREF was assessed in Weeks 0 and 6.	Unclear if assessors were aware of intervention received by participants. No protocol record and not registered in trial database. Paroxetine is a SSRI which is in line with NICE pathway for GAD (although NICE recommends sertraline as first line treatment). BNF dose is 20 mg daily for GAD and SAD. No ethical approval described.
Non-comparative studies (before and after design)				
Bystritsky et al. (2008) USA n=12	**Design:** Single-arm, open label cohort pilot study. **Intervention:** Alpha-Stim SCS. At the initial visit the investigator set the sensory threshold for each patient, then the patient was instructed to self-administer consistently at home for 1 hour daily between 3pm to 7pm for a total of 6 weeks. **Control:** None.	**Participants:** Adults with diagnosed GAD. **Setting:** Patients recruited from University of California, LA Anxiety Disorders Program at the Semel Institute for Neuroscience and Human Behaviour. Outpatient setting in the USA.	**Primary:** Change in the HAM-A from baseline to 6 weeks. Response to treatment was defined as a reduction in ≥50% on HAM-A and a CGI-I score of 1 or 2. Symptom remission was CGI-I score of 1 or 2 and a score of ≤7 on HAM-A. **Secondary:** Assessments included Clinical Global Impressions-severity of illness (CGI-S) (beginning at week 2) and the HAM-D-17. Patients also completed the Patient Global Impressions-Improvement (PGI-I) scale and the Four-	No control group. At risk of bias as patients assess their own symptoms. Small sample size (pilot study). 9 patients (75%) completed the study. 25% loss to follow-up. ITT analysis using last observation carried forward.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
	Funding: Funding provided by Saban Family Foundation. The Alpha-Stim Stress Control System devices were loaned to the subjects free of charge by Electromedical Products International. **Status:** Published.		Dimensional Anxiety and Depression Scale (FDADS). **Follow-up:** Study visits were conducted at baseline and at the end of 3 and 6 weeks of treatment.	
Morris et al. (2019) England n=161	**Design:** Single-arm, open-label, study with economic evaluation. **Intervention:** (n=161) Alpha-Stim AID. Participants offered 60 min per day at a current of 100 µA per day for 6 consecutive weeks. Device not locked. Participants could choose to continue treatment for 6 weeks (12 weeks total). If participants started iCBT during the 6–12 weeks of Alpha-Stim, they could continue with Alpha-Stim while receiving iCBT at the same time. Similarly general practitioners could independently decide to place the patient on medication for GAD at the same time as participants	**Participants:** Treatment seeking patients with GAD diagnosis who had not responded to computerised CBT or bibliotherapy over 24 weeks, and were waiting for iCBT for GAD (n=161 enrolled). GAD in combination with a comorbid depression or other anxiety disorder allowed. **Setting:** 2 NHS Improving Access to Psychological Treatment (IAPT) services in England.	**Primary:** Proportion of participants who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7. **Secondary:** Personal Health Questionnaire (PHQ-9) at 12 and 24 weeks, Athens Insomnia Scale (AIS) at 12 and 24 weeks, Work and Social Adjustment Scale (WASA) at 12 and 24 weeks, EQ5D-5L at 12 and 24 weeks. Other key outcomes are the proportion of cases who meet a clinically important ("reliable improvement") 5 point improvement on the GAD-7 at 12 and 24 weeks, the proportion who meet criteria for recovery (GAD-7 score of 7 or less and also exhibiting a 5 point drop in GAD-7 score) at 12 and 24 weeks,	No control group (before-after design). Open label, at risk of bias as patients assess their own symptoms. GAD-7 questionnaire self-administered. Large number of patients (78%) declined to participate. 30% withdrew from treatment at 12 weeks. 50% withdrew from follow-up. Missing completely at random (MCAR) assumption used and data imputed. ITT analysis used. Difficult to know how many patients completed each questionnaire because data imputed. Patient who started iCBT during Alpha-Stim treatment could receive both (80 patients (50%) had iCBT, although later the authors say 25 patients had CES & iCBT).

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
	continued to receive Alpha-Stim. **Control:** none. **Funding:** Electromedical Products International (but had no role in design, conduct, reporting). **Status:** Published study.		and the effect size of the change in GAD-7 score over 12–24 weeks. **Follow-up:** Clinical outcome and QoL measure were collected at 4, 6, 8, 12 and 24 weeks by e-mail, telephone or post according to participant preference.	Funded by company.
Overcash (1999) USA n=197	**Design:** Retrospective, before and after study. **Intervention:** Alpha-Stim Cranial electrotherapy stimulation (CES) was used for about half the sessions (25 minutes) at a 0.05Hz frequency and a comfortable current setting up to 500 µA. Often patients were placed in a "Relax and Learn Room" where they watched videotapes of relaxing scenery and listened to superlearning music. Over 80% of the time patients were loaned an Alpha-Stim to take home and use once or twice a day in a manner consistent with how they were using it successfully in the clinic.	**Participants:** Patients diagnosed with anxiety disorder and treated at author's clinic. Most patients reported very high levels of anxiety for past 2 months. All but 6 patients were referred by local physicians in the area (n=197 began treatment, 182 completed treatment). **Setting:** Outpatient private practice in the USA.	Subjective self-rating of anxiety symptoms (0-100). Electromylegram (EMG) Electrodermal response (EDR) Peripheral temperature (TEMP). **Follow-up:** Psychophysiological and subjective measurements of anxiety were made before and after treatment. Length of treatment not reported.	Retrospective study with no control group. Open label, at risk of bias as patients assess their own symptoms. Eligibility criteria not described. No sample size calculation. Subjective and non-validated self-reporting outcome measure. Variable intervention and used alongside other non-study interventions. 92% of participants completed study. No ITT analysis. No ethical approval described.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
	Control: None. **Funding:** Not reported. **Status:** Published			
Unpublished studies (the author died)				
Voris (1995) **UNPUBLISHED** USA n=105 (60 with anxiety scores)	**Design:** Triple blind randomised controlled study. **Intervention:** Alpha-Stim 100 at 300 µA and 0.5 Hz for 20 minutes during regular therapy group (number of treatments not reported, description of usual therapy not given) (n=38; 31 with State-Trait Anxiety Inventory , STAI score). **Controls:** Sham device (n=14 with STAI score) or no treatment (n=15 with STAI score). **Funding:** Not reported. **Status:** Unpublished	**Participants:** Individuals drawn from a general psychiatric population suffering from a clinically significant anxiety dysfunction (incl. agoraphobia, GAD, panic attacks, OCD, asocial phobia, simple phobia). **Setting:** Delos Mind/Body Institute, USA.	**Outcomes:** State Trait Anxiety Inventory (STAI) EMG Skin temperature **Follow-up:** Not reported. Report says that over a period 10 days all of the groups that worked with stress or anxiety were tested. Measurements were recorded before and immediately following treatment.	Non-peer reviewed report (available on company website). Unclear description of population. Eligibility criteria not described. Inclusion of data from patients without diagnosed anxiety disorder. Active group included patients with manic-depression, psychosis, major depression, all of which demonstrated significant anxiety. These conditions are out of scope, therefore the generalisability of the results may be limited. No sample size calculation. Randomisation based on seats in therapy room (not truly random as element of patient self-selection). Number of Alpha-Stim treatments given not reported. (Information from the company suggests that outcomes were measured after a single Alpha-Stim session). Description of usual therapy not given. Only 60 of 105 randomised participants were included in

Study name and location	Design and intervention(s)	Participants and setting	Outcomes & follow-up	EAC comments
				the analysis because patients who did not meet anxiety criteria based on pre-treatment STAI scores were excluded during analysis of the data.

4.2 Summary of economic evidence

The company and the EAC identified 1 relevant economic study of Alpha-Stim AID (Morriss et al. 2019). An unpublished MSc thesis was excluded by the EAC because it had low applicability to the NHS setting.

The Morriss et al. (2019) study is described in the table 1 above. It was conducted in 2 NHS Improving Access to Psychological Treatment (IAPT) services and used a cost minimisation approach to determine the cost impact of introducing Alpha-Stim AID as a treatment option. Results of the study suggested that using Alpha-Stim AID saved £540.9 per patient compared with individual cognitive behavioral therapy (iCBT). The EAC considered the study was of poor methodological quality.

De novo analysis

The company submitted a simple decision tree model (Figure 2 in section 9.2 of the Assessment report, page 62), where people either received Alpha-Stim AID up to 12 weeks or one course of individual CBT (iCBT) (8 sessions). Patients who do not respond to iCBT receive another course of iCBT and those that do not respond to Alpha-Stim receive up to 2 courses of iCBT. The company developed its cost model with a time horizon of 6 months (24 weeks) and the EAC considered this was appropriate.

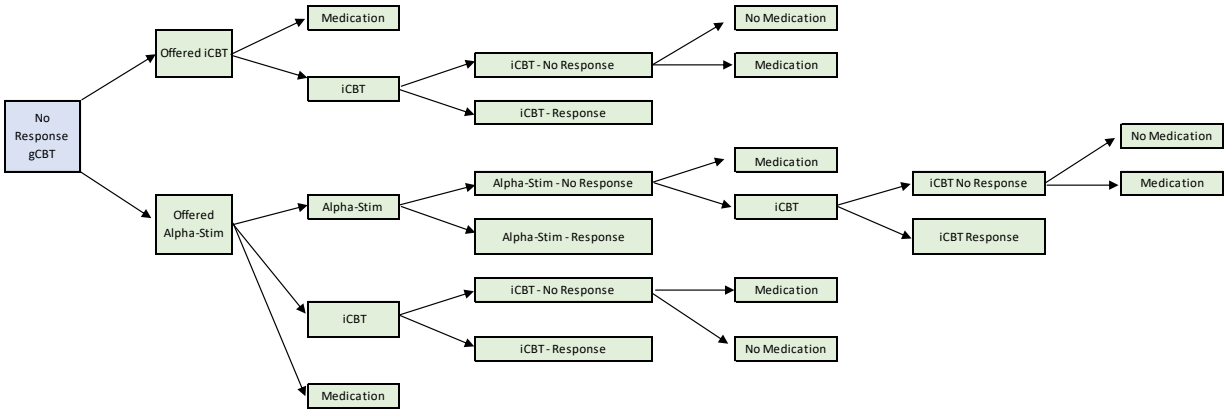
EAC revisions to the model

The EAC considered the assumptions were generally justified but noted that a significant proportion of patients offered Alpha-Stim AID chose not to use it and instead waited for iCBT (Morriss et al. 2019). Morriss et al. (2019) commented that this rate of uptake was in response to 'cold calling' patients by telephone to offer Alpha-Stim AID as therapy, and that uptake may be higher if Alpha-Stim AID is offered as routine practice. The EAC adjusted the company's model to reflect the uptake for Alpha-Stim AID reported by Morriss et al. (2019) (see Figure 3 in section 9.2 of the assessment report, page 63).

The EAC also presented a decision tree as its base case which reflects the clinical experts' opinions of the current care pathway. This decision tree includes only 1 course of iCBT per patient and includes medication as an option at the start of the

pathway and also as an option for no responders after Alpha-Stim AID or iCBT (see Figure 1)

Figure 1: EAC base case decision tree model



Model parameters

The parameters included in the company model are response rates for Alpha-Stim AID and iCBT. Response rates for the Alpha-Stim were based on an empirical study of a series of 161 participants recruited from 2 NHS organisations (Morriss et al. 2019). Response rates for iCBT are taken from published literature (Gyani et al, 2013). The EAC did not change these parameters.

The EAC adjusted company's model assumed 22% of patients would choose Alpha-Stim AID based on the results from Morriss et al. (2019).

The EAC's base case model assumed 15% of patients would choose medication in preference to treatment with either iCBT or Alpha-Stim AID. In addition, it assumed 50% of non-responders to an intervention (iCBT or Alpha-Stim) would choose medication. The model did not include any response to medication. The model included the reduced uptake for Alpha-Stim (22%) in the intervention arm.

Costs and resource use

The cost of Alpha-Stim AID in the company's submission is calculated as £70 per patient. This is based on a unit cost of £450.00 (excluding VAT) for the device and an assumed utilisation by 15 patients over an average product lifetime of 3 years (based on 10-week sole use per patient). This usage allows for losses which are

estimated to reduce average product lifetime by 2 years from the 5-year warranty lifetime. Additional costs per patient including therapist time, postage and consumables were estimated at £40, yielding £70 per duration of the treatment per patient.is £70. The EAC considered this cost per patient appropriate. The EAC uplifted the cost of standard practice iCBT from £887.86 to £899.92 per cycle (8 sessions) and used a cost of £127.24 for 6 months use of sertraline.

Results

Base case results

The company submission estimated a cost saving of £817.68 per patient with Alpha-Stim AID. The EAC considered that this was a simple cost difference between the cost per patient using Alpha-Stim and iCBT and was not an incremental cost per-patient, which needs to include the cost of subsequent treatments for patients who do not respond to the initial treatment. The EAC therefore re-calculated the company base case to be a saving of £540.88 per patient over 6 months compared to iCBT.

The adjusted company's base case which reflected the reduced uptake of Alpha-Stim AID, where only 22% of those offered the treatment chose it, showed that Alpha-Stim AID saved £120.85 per patient over 6 months compared with iCBT. The EAC's base case that included medication as a treatment option and the reduced uptake of Alpha-Stim showed that using Alpha-Stim AID saved £80.79 per patient compared with iCBT.

Scenario analysis

The EAC also explored 3 scenarios based on expert advice about the clinical pathway:

- Scenario 1 uses the EAC base case: all patients in the Alpha-Stim AID arm who do not choose medication, choose Alpha-Stim AID before iCBT. Alpha-Stim AID non-responders move to iCBT or medication.
- Scenarios 2 is based on the adjusted company base case: 50% of non-responders go on to have a second cycle of iCBT and the response rate is reduced from 54.2% to 50%.

- Scenario 3 is based on the EAC base case: patients who do not respond to iCBT, a proportion will choose to move straight to medication (15%) and of the remaining patients, 22% will choose Alpha-Stim AID before moving medication.

Table 3 - Summary of results.

Alpha-Stim AID (per patient)	iCBT (per patient)	Cost saving per patient
Company base case		
£753.35	£1,294.23	£540.88
Adjusted company model (22% of patients in intervention arm choose to use Alpha-Stim)		
£1,191.24	£1,312.08	£120.85
EAC base case (15% of patients choose medication in both arms, no 2nd iCBT, 50% non-responders in both arms choose medication, 22% of patients in Alpha-Stim arm choose Alpha-Stim)		
£728.00	£808.79	£80.79
Scenario 1 (EAC base case but with all patients who are offered Alpha-Stim choose it.)		
£441.57	£808.79	£367.22
Scenario 2 (Adjusted company model, reduced response for 2nd iCBT from 54.2% to 50.0%)		
£1,008.75	£1,106.00	£97.25
Scenario 3 (EAC base case but 22% patients who are non-responders to iCBT as first treatment option in the intervention arm will choose to try Alpha-Stim before medication)		
£720.36	£808.79	£88.43

Sensitivity analysis

Results of the company probabilistic sensitivity analysis suggest that Alpha-Stim AID is cost saving in 99.9% of iterations. The EAC performed deterministic sensitivity analysis which showed that in the EAC base case, the cost of iCBT which was reflective of the number of sessions of iCBT (ranging from 2 to 20 sessions) and the uptake of Alpha-Stim AID were the key drivers impacting the results. Details of sensitivity analysis by the company and the EAC were described in section 9.3 of the assessment report (page 77 to 79).

The EAC concluded that Alpha-Stim AID is cost-saving compared with iCBT in all scenarios. but the extent of the cost benefit is dependent on the number of patients choosing to use Alpha-Stim and avoiding iCBT as well as on the cost of delivering iCBT.

5 Patient survey

NICE's public involvement programme circulated a survey to explore people's experience using Alpha-Stim AID between June and July 2020. A total of 824 responses were received. Results from responders who have been diagnosed with anxiety related conditions and who were prescribed the device by a doctor (n=270) were extracted and are summarised Appendix C.

The majority of responders reported an improvement in managing anxiety after using the device (n=240), and positive impacts that were commonly stated included:

- More or better control of daily life
- Becoming calm and reduction in anxiety
- Improvement in quality of life
- Come off medication
- Sleep better
- Help managing depression
- Reduction in pain
- Generally feel better

Some responders (n=19) stated that they also used other medical devices that were similar to Alpha-Stim AID and thought that Alpha-Stim AID worked better, was easier to use and provided faster calming effect compared with other devices.

A few responders (n=8) thought their anxiety symptoms had little improvement after using the device. Three responders reported issues related to the device included the cost of batteries and the weight of Alpha-Stim AID. A proportion of responders (27%, n=71) reported complications experienced while using the device including:

- Discomfort (ear)
- Feeling of dizzy or sickness
- Headache
- Feeling hyper (hard to sleep)
- The level of frequency may vary (need more guidance)
- Worsening depression or anxiety
- Inaccurate Battery gauge
- Hard to get replacement

- Others for example unusual physical sensations around head and neck

6 Ongoing research

The company referred to an ongoing study (Royal et al. 2020) with the EAC, and provided preliminary results of the study This is a UK non-randomised study, which aims to evaluate the effectiveness of a new treatment pathway in primary care designed to optimise the patient experience without increasing the cost burden. Study participants are attendees at a nurse-led clinic for people who have mental health problems. All people in the study had either an anxiety disorder or mixed anxiety and depression diagnosed at assessment with the clinician. The planned sample size is 100 and the preliminary results provided by the company were “initial” and “current” GAD-7 and PHQ-9 scores from 51 participants of the study. The EAC reviewed and critiqued the study (see details in the EAC addendum report). It concluded that the study suggested that Alpha-Stim AID could be used to treat anxiety however there are some concerns regarding the applicability and generalisability of the study at this time; for example, selection bias. The EAC did not identify any other ongoing trials in the search.

7 Issues for consideration by the Committee

Clinical evidence

The evidence base included 3 RCTs and 3 observational studies but quality of the included studies is poor. Most included studies are non-UK studies and only 1 non-comparative study was done in the NHS setting, therefore the generalisability of the results may be limited.

Three RCTs showed statistically significant improvements in anxiety scores in adults treated with Alpha-Stim AID for generalised anxiety disorder compared with those of the control group (paroxetine, sham device, or no treatment). The EAC considered that the treatment effect observed in RCTs may be reduced in a real-life NHS setting when implemented in clinical practice for reasons such as concomitant use of other therapies, differences in study sample versus larger population, patient adherence to treatment programme, and clinician preference.

The EAC considered that the evidence base supports the short-term clinical efficacy of Alpha-Stim AID as a treatment option for generalised anxiety disorder. But the long-term benefit is unclear because the longest follow-up was in Morris et al. 2019, which suggested that anxiety symptom improvements were sustained at 24 weeks.

Current standard of care for people with anxiety disorder at step 3 includes individual high-intensity psychological interventions (such as individual CBT (iCBT) or individual applied relaxation) or a drug treatment. There is no direct comparison between Alpha-Stim AID and individual high-intensity psychological interventions such as iCBT. One RCT showed an improvement in anxiety symptoms in patients treated using Alpha-Stim AID and the drug (paroxetine) compared with paroxetine alone.

As well as IAPT services, Alpha-Stim AID could also be used for the treatment of anxiety disorders in GP practices and in secondary care settings. There is an ongoing study of its use in GP practices which has reported preliminary academic-in-confidence results and no evidence available yet for its use in secondary care settings.

Cost evidence

The cost models suggest that Alpha-Stim AID is likely to be cost-saving compared to iCBT. The main driver of the cost saving is the proportion of patients who choose to use Alpha-Stim with higher uptake of the device leading to greater cost savings. There is limited information available for the update rate of Alpha-Stim AID. The number of iCBT sessions required is also likely to have a significant impact on potential cost-savings as the fewer sessions of iCBT required the lower the cost of iCBT. The EAC adjusted the company base case to reflect the uptake of Alpha-Stim AID and also presented its own base case to current care pathway. But the EAC noted that the clinical scenario is likely to be a complex mix of treatments with some patients taking medication as well as iCBT or Alpha-Stim treatment, some patients having a preference for medication and some patients having a preference for non-pharmacological treatments.

The EAC is aware that there is currently a study ongoing in the primary care setting which potentially includes an economic analysis however there is no data available

for review during this assessment (see section 8.2 of the assessment report, page 56).

8 Authors

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Bernice Dillon, Health technology assessment adviser

NICE Medical Technologies Evaluation Programme

August 2020

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

A Details of assessment report:

Dr Judith White, Dr Helen Morgan, Dr Laura Knight, Dr Susan O'Connell, Andrew Cleves, Prof Grace Carolan-Rees. Cedar health technology research centre.

B Submissions from the following sponsors:

Electromedical Products International, Inc

C Related NICE guidance

- Generalised anxiety disorder and panic disorder in adults. NICE clinical guideline 113 (2019). Available from https://www.nice.org.uk/guidance/cg113
- Social anxiety disorder: recognition, assessment and treatment. NICE clinical guideline 159 (2013). Available from https://www.nice.org.uk/guidance/cg159
- Common mental health problems: identification and pathways to care. NICE clinical guideline 123 (2011). Available from https://www.nice.org.uk/guidance/cg123

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Lu L and Hu J (2014) A comparative study of anxiety disorders treatment with Paroxetine in combination with cranial electrotherapy stimulation therapy. Medical innovation of China, 11 (8): 80-82.

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Morriss R, Xydopoulos G, Craven M et al. (2019) Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder. Journal of Affective Disorders 253, 426-37.

Overcash S J (1999) Cranial electrotherapy stimulation in patients suffering from acute anxiety disorders. American Journal of Electromedicine 16(1), 49-51.

Voris D (1995) An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among outpatient psychiatric patients, impulse control parolees and pedophiles. Delos Mind/Body Institute Newsletter.

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.

- Chris Griffiths, Senior Research and Evaluation Fellow, Innovation and Research Department Northamptonshire Healthcare NHS Foundation Trust.
- Karina Lovell, Director of research division of nursing, midwifery & social work, school of health science, faculty of biology, Medicine and Health, University of Manchester.
- Cynthia Fu, Honorary Consultant Psychiatrist in the National Affective Disorders Service, South London and Maudsley NHS Foundation Trust; University of East London.
- Richard Morriss, Professor of Psychiatry & Community Mental Health, Faculty of Medicine & Health Sciences, University of Nottingham.
- Simon Royal, Honorary Assistant Professor Primary Care, University of Nottingham.
- Caroline Stevens, CBT (therapist), Nottinghamshire Healthcare Foundation NHS Trust.
- James Kustow, Consultant Psychiatrist, Enfield and Haringay Mental Health NHS Trust
- Roz Shafran, Professor of Translational Psychology, UCL Great Ormond Street Institute of Child Health

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

Appendix C: Results from the patient survey

From 11 June to 9 July 2020, NICE's public involvement programme sent a survey to patient organisations and also posted it via the social media platform, Twitter. A total of 824 responses were received.

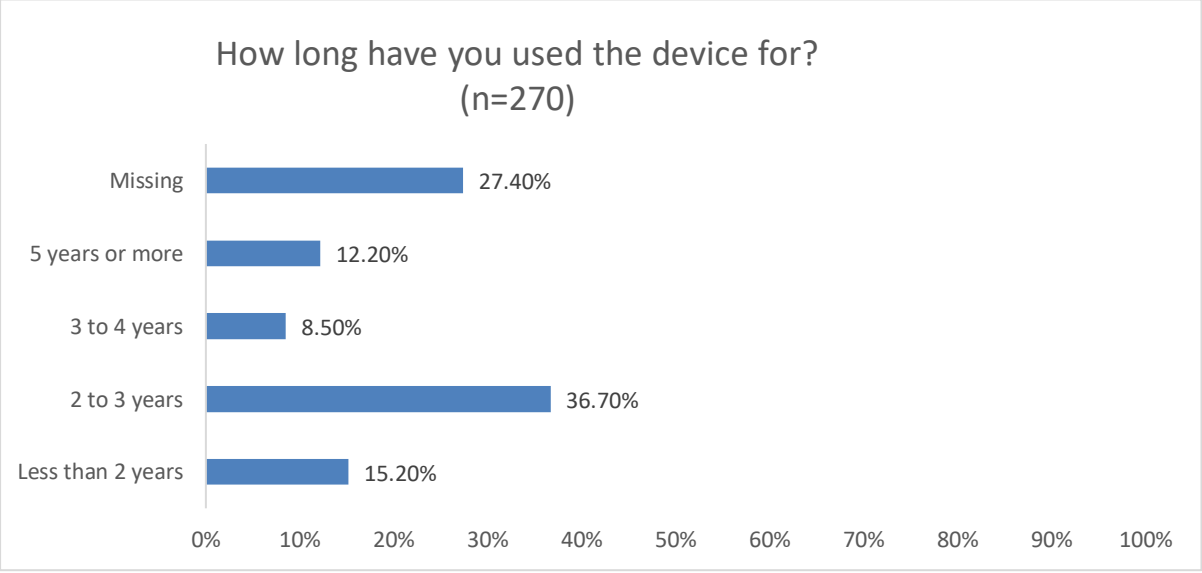
All responders confirmed that they read the information sheet provided which explains the purpose of the survey and how the information will be used. All responders consented to NICE using their information as described.

Of people responded, people used the device for anxiety, depression, insomnia and pain management. Sixty-one percentage of the responders (n=501) were diagnosed with an anxiety related conditions including generalised anxiety disorder (GAD), social anxiety disorder, obsessive-compulsive disorder (OCD) or a phobia. Responders accessed to the device via various methods such as a doctor's prescription, recommendations by other people, advertisements, charities or others. Results in this summary focused on responders who have been diagnosed with anxiety related conditions and who were prescribed the device by a doctor (n=270).

1. Device usage

Responders stated that they used the device every day, some responders used the device twice daily with some stating that they use it more frequently depending on their anxiety levels. Most responders wore the device ranging between 20 and 60 minutes for each session, and a few responders (n=6) had the device more than 60 minutes each session. Responders stated that they have used the device for 1 to 3 years, and a small proportion of responders used for 5 years or more (12.2%). Five responders have used Alpha-Stim for 15 years or more.

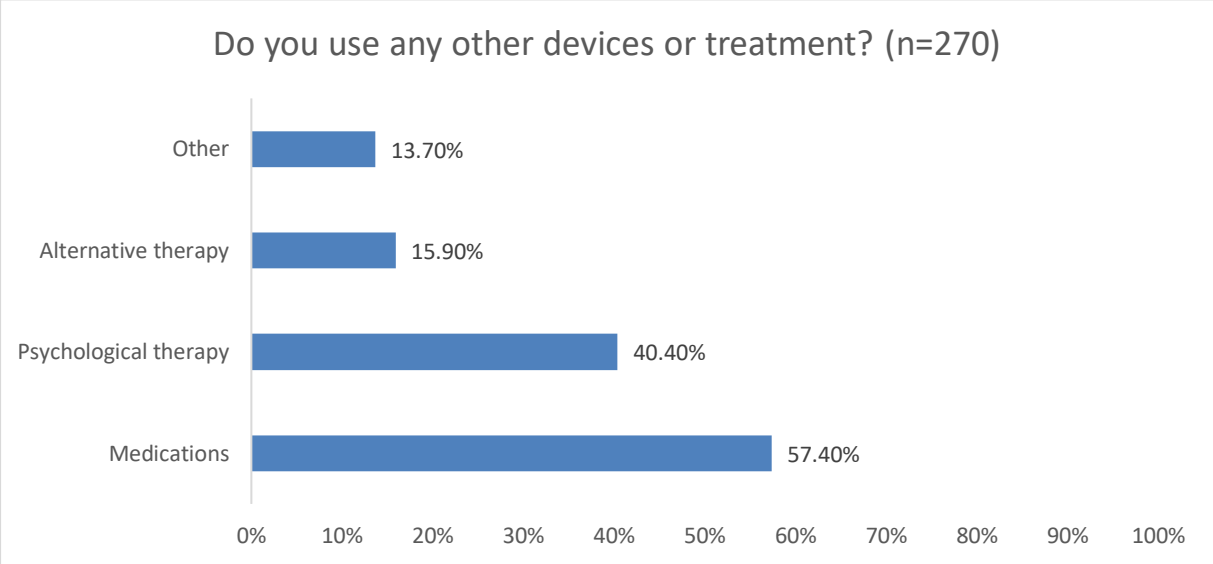
How long have you used the device for? (n=270 responders)



2. *Other /treatments*

Responders stated they also used other treatments for anxiety including medications, psychological therapy, alternative therapy and others.

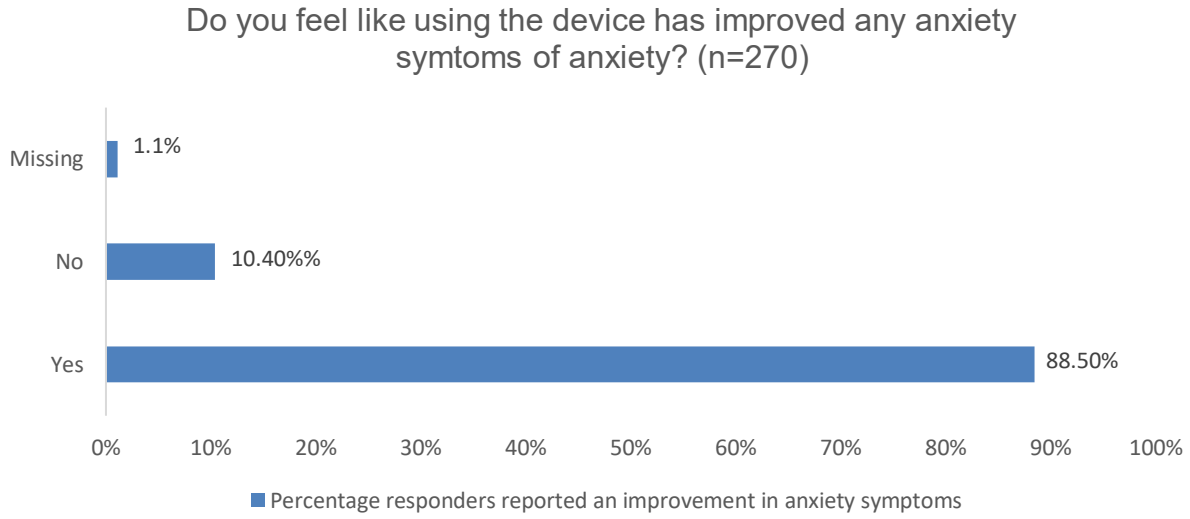
Do you use any other devices or treatment? Please select all that apply



Some responders (n=19) stated that they also used other medical devices that were similar to Alpha-Stim such as neuro feedback, TENS unit, Proteus, Bellabee, EMDR (eye movement desensitization and reprocessing), Fisher-Wallace Cranial Stimulator device. These responders thought that Alpha-Stim worked better, easier to use and provided faster calming effect compared with other devices.

3. *Effectiveness of device*

Responders reported their anxiety symptoms were improved after using the device.



4. Patient experience statement

Does Alpha-Stim AID have any positive effects for you, your condition and/or your quality of life?

The majority of responders shared their positive experience using the device (n=240). Table 1 (see below) summarised main themes reported by responders and illustrated by patients' statements:

Table 1: Positive effects of Alpha-Stim AID

Theme	Patient statements
More or better control of daily life	I am able to change the course of a stressful day and not allow the entire day to be swept away in the torrent of anxiety.
	It helps take the edge off mild to medium anxiety in the moment, so I don't have to take another prescription medication. And long term it helps with mood stability.
	It has changed the way I am able to react to anxiety producing situations. It's hard to describe but I have less noise to deal with. It's easier to regulate my emotions. I am able to calm myself easier and remember all I can control are my reactions. I fall asleep and stay asleep easier. I feel very blessed to have been introduced to Alpha-Stim. My best friend also benefitted and has a device on order.
Becoming calm and reduction in anxiety	Each time I have the device on me for 1hr, I feel relaxed, my pain flur ups disappear and the anxiety calms down.
	My anxiety goes down tremendously after using Alpha-Stim.
	Marked decrease in both anxiety and depression, increased feeling of calm
	Huge positive impact. When I first had an anxiety meltdown about 10 years ago, I was basically in a constant state of panic attack for about 6 months. Tried all different types of meds to control to no avail. Got on the device, and I saw immediate positive results. I still use it to this day when my symptoms get out of control.
Improvement in quality of life	Improved quality of life because I have a solution for the times when anxiety might turn into a panic attack or something to greatly reduce a panic attack.
	It has given me the chance to have a more normal quality of life most of the time. My anxiety is much less severe than it used to be. The device has really improved my generalised anxiety disorder. It has no side effects and the benefits to me have been huge.
	Taking meds made me feel like an zombie, now I can focus on enjoying life.

Come off medication	This device has helped me take less anxiety medication. I feel like I have control over my anxiety now. Just knowing that I can us the Alpha Stim anytime I am overwhelmed is a relief. I normally use it just at night but I have occasionally used it during the daytime when I have needed it.
	Was able to wean off my daily Klonopin and antipsychotic for anxiety and depression using Alpha Stim (with my psychiatrist's help)
Sleep better	I sleep so much better with regular use of the device. So I feel much better during the days, and am more engaged in my life, rather than holding back more because of anxiety.
	I sleep better, I have less panic attacks, I am less irritable, my depression is reduced. If it could take away my pain then it would be the perfect device, but still life changing.
	No more panic attcks. I sleep better and i feel calm.
Help managing depression	I have had anxiety and depression since childhood. Use of the Alpha stim is the only thing that works for my depression and anxiety. I really can't imagine life without it.
	Motivates me; supports me; increased ability to accomplish; less symptoms of depression & anxiety if maintained.
Reduction in pain	I began using this to treat multiple areas of pain and followed the probes up with brain treatments. It significantly reduced my pain and my anxiety.
	Positive also helping manage pain level. Have been able to cut pain meds done to maybe once a day. To some days none at all. Still take anxiety meds at nite only.
Generally feel better	I feel..... , sometime is better but sometime is down. but most of time, I feel better when I used it.
	I feel a little better, I still have my moments but it's better than before. My condition is still lattice but my quality of life is better

Does Alpha-Stim have any negative effects for you, your condition and/or your quality of life?

The majority of responders did not report any experience of a negative effect using the device (n=238). A few responders (n=8) thought their anxiety symptoms had little improvement after using the device. Three responders reported issues related to the device including:

- The weight of the device: 1 responder thought that “A device is little bit heavy, so can you make more less weight”.
- Batteries: 1 responder stated that the cost of batteries could be expensive and another responder stated that “Having to buy batteries more, wish they made a rechargeable unit”

Have you experienced any complications from using the device? Or unwanted effects?

Of 259 responders who answered the question, 71 (27.4%) reported complications from using Alpha-Stim. Complications reported by responders included:

- Discomfort (ear)
- Feeling of dizzy or sickness
- Headache
- Feeling hyper (hard to sleep)
- The level of frequency may vary (need more guidance)
- Worsening depression or anxiety
- Inaccurate Battery gauge
- Hard to get replacement
- Others for example unusual physical sensations around head and neck

Just under 50% of responders (n=231) who have been diagnosed with anxiety related condition had the device via recommendation, advertisement, charity organisations and other means. An overview of the survey results of these responders suggested that their experience were similar to those who accessed the device through doctor prescription. Most of responders used Alpha-stim once or twice daily for around 20 to 60 minutes. Eighty percentage (n=184) of responders felt the use of Alpha-stim had a positive impact on their

anxiety symptoms. In addition to the complication reported, a few responders suggested using Alpha-Stim made them feel anxious.

Appendix D: decision problem from scope

Population	People with anxiety disorders	
Intervention	Alpha-Stim AID as a stand-alone intervention or as an additional treatment to psychological interventions	
Comparator(s)	• Pharmacological interventions (e.g. selective serotonin reuptake inhibitors) • Psychological interventions (e.g. self-help, group or individual CBT)	
Outcomes	The outcome measures to consider include: • Anxiety and depression symptoms scores • Use of psychological interventions • Use of pharmacological interventions • Number of GP visits • Waiting time for psychological treatments • Pharmacological related adverse events such as overdose • Patient quality of life measures • Treatment compliance • 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 long enough to reflect 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	• People who also have other mental health disorders such as depression • People with other comorbidities (i.e. chronic physical conditions such as diabetes or cardiovascular disease) • Severity of anxiety (e.g. anxiety disorder assessment)	
Special considerations, including those related to equality	The condition can have a significant effect on individuals' daily lives. This may mean someone is disabled if their anxiety disorder has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act. People from certain socially excluded groups that would benefit from psychological interventions might be less likely to access them, such as black and minority ethnic groups; older people; those in prison or in contact with the criminal justice system; and ex-service personnel. Young women are more likely to have anxiety disorder. Sex and age are all protected characteristics under the Equality Act 2010	
Special considerations, specifically related to equality	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 characteristic?	No

	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 the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	No	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Alpha-Stim AID for anxiety disorders

1 Technology

1.1 Description of the technology

Alpha-Stim AID (Electromedical Products International, Inc) is an electrotherapy device for managing anxiety, insomnia and depression. This scope focuses on the use of Alpha-Stim AID for anxiety disorders. The technology was developed in 1981 in the US, and Alpha-Stim AID is the latest model.

Alpha-Stim AID uses cranial electrotherapy stimulation (CES), by providing a variable electrical microcurrent to the brain which stimulates alpha wave electrical activity. The current has a pulse repetition rate of 0.5 hertz and is composed of bipolar asymmetric rectangular waves in a cycle that repeat periodically at 10 second intervals.

Alpha-Stim AID is the size of a mobile phone and has a pair of small clips with removable soft pads that need to be moistened with a solution which conducts electricity. The current is applied by these clips that attach to the ear lobes and the strength of the current can be adjusted. Alpha-Stim AID is recommended to be used for between 20 and 60 minutes every day, every other day, or on an as-needed basis. Alpha-Stim AID is battery powered, which allows users to be mobile when using it.

Alpha-Stim AID is not suitable for people with cardiac pacemakers and implanted defibrillators. The technology may be suitable for use during pregnancy. Children should use Alpha-Stim AID under adult supervision.

1.2 Relevant diseases and conditions

Anxiety disorders are common mental health conditions and include generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder (PTSD), panic disorder, obsessive–compulsive disorder and body dysmorphic disorder. There is considerable variation in the severity of anxiety disorders, and some are associated with significant long-term disability. They can be distressing for the person affected, their families, friends and carers, and can have an impact on their local communities. Anxiety disorders can have a lifelong course of relapse and remission.

In the UK in 2010, 8.2 million adults were diagnosed with an anxiety disorder and the cost of treatment for the anxiety disorder was estimated to be £11,687 for each adult, and it is one of the most costly psychiatric and neurological disorders (Fineberg et al. 2013). An adult psychiatric morbidity survey in England reported that the 1-week prevalence of generalised anxiety disorder was 6.6% and anxiety disorders were more common in women than in men, with the most apparent difference in those aged between 16 and 24 (respectively GAD 9.0%; phobias 5.4%; OCD 2.4%; and panic disorder 2.2%) than in other age sex groups (McManus et al. 2014).

1.3 Current management

NICE's guideline on generalised anxiety disorder and panic disorder in adults provides principles of care for people with generalised anxiety disorder (GAD). It also recommends a stepped-care model to organise service provision and to help people with GAD, their families, carers and practitioners to choose the most effective intervention.

NICE's guideline on social anxiety disorder: recognition, assessment and treatment provides treatment principles for treating adults with social anxiety disorder. It recommends that individual cognitive behavioural therapy (CBT) that has been specifically developed should be offered to adults with social anxiety disorder. If the person wishes to proceed with a pharmacological intervention, a selective serotonin reuptake inhibitor (SSRI) (escitalopram or sertraline) should be offered. For adults who decline cognitive behavioural and

pharmacological interventions, short-term psychodynamic psychotherapy that has been specifically developed to treat social anxiety disorder should be considered. The guideline also provides recommendations on interventions for children and young people with social anxiety disorder. Pharmacological interventions should not be offered to treat social anxiety disorder in children and young people.

NICE's guideline on post-traumatic stress disorder (PTSD) provides recommendations on management of PTSD including active monitoring, psychological-focused debriefing, psychological interventions and drug treatment. Drug treatments are not recommended for the prevention or treatment of PTSD.

NICE's guideline on common mental health problems: identification and pathways to care describes a stepped-care model for organising the provision of services and helping people with common mental health disorders, their families and healthcare professionals to choose the most effective interventions. Common mental health problems included in this guideline are: general anxiety disorder, depression, panic disorder, obsessive compulsive disorder and post-traumatic stress disorder.

1.4 Regulatory status

Alpha-Stim AID was CE marked as a class IIa medical device in 2012.

A search of the Medicines and Healthcare products Regulatory Agency website shows no manufacturer field safety notices or medical device alerts for the technology.

Claimed benefits

The benefits to people with anxiety disorders claimed by the company are:

- Improvement in anxiety and depression symptoms
- Increased treatment choices for people with anxiety disorders
- An alternative management to pharmacological and/or psychological interventions which do not always work or are not desired by everyone with anxiety disorders

- Additional benefit when combined with psychological interventions
- An alternative option to be used in people with medical co-morbidity and disability who might not be able to travel to appointments or tolerate medication
- Home use for the potential reduction in time and cost associated with attending appointments

The benefits to the healthcare system claimed by the company are:

- Reduced cost when comparing with intensive psychological treatment such as individual CBT (iCBT)
- Reduced use of healthcare resources; for instance reducing GP visits or outpatient visits
- Reduced cost in treating complications of medication use such as overdose

2 Decision problem

Population	People with anxiety disorders
Intervention	Alpha-Stim AID as a stand-alone intervention or as an additional treatment to psychological interventions
Comparator(s)	• Pharmacological interventions (e.g. selective serotonin reuptake inhibitors) • Psychological interventions (e.g. self-help, group or individual CBT)
Outcomes	The outcome measures to consider include: • Anxiety and depression symptoms scores • Use of psychological interventions • Use of pharmacological interventions • Number of GP visits • Waiting time for psychological treatments • Pharmacological related adverse events such as overdose • Patient quality of life measures • Treatment compliance • 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 long enough to reflect 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	• People who also have other mental health disorders such as depression • People with other comorbidities (i.e. chronic physical conditions such as diabetes or cardiovascular disease) • Severity of anxiety (e.g. anxiety disorder assessment)	
Special considerations, including those related to equality	The condition can have a significant effect on individuals' daily lives. This may mean someone is disabled if their anxiety disorder has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act. People from certain socially excluded groups that would benefit from psychological interventions might be less likely to access them, such as black and minority ethnic groups; older people; those in prison or in contact with the criminal justice system; and ex-service personnel. Young women are more likely to have anxiety disorder. Sex and age are all protected characteristics under the Equality Act 2010	
Special considerations, specifically related to equality	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 characteristic?	No
	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 the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	No	

3 Related NICE guidance

Published

- Anxiety disorder (2014) NICE quality standard [QS53].
- Common mental health problems: identification and pathways to care (2011). NICE guideline [CG 123].
- Generalise anxiety disorder and panic disorder in adults (2019) NICE guideline [CG113].
- Obsessive-compulsive disorder and body dysmorphic disorder (2005) NICE guideline [CG31].
- Post-traumatic stress disorder (2018) NICE guideline [NG 116].

Social anxiety disorder: recognition, assessment and treatment (2013). NICE guidance [CG159].

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association of British Neurologists
- Association of Neuroscience Nurses
- Brain Research UK
- British Association for Counselling and Psychotherapy
- British Association of psychotherapists
- British Pain Society
- British Psychological Society
- British Psychotherapy Foundation
- College of Mental Health Pharmacy
- Counsellors and Psychotherapists in Primary Care
- Institute of Neurology
- Primary Care Mental Health Education
- Primary Care Neurology Society
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of Nursing

- Royal College of Physicians
- Royal College of psychiatrists
- Society of British Neurological Surgeons
- The Association of Neurophysiological Scientists
- United Kingdom Council for Psychotherapy

4.2 Patient

NICE's Public Involvement Programme suggested the following organisations for patient commentary on the use of Alpha-Stim AID during the guidance development::

- Anxiety alliance
- Anxiety UK
- Aware defeat depression
- Big white wall
- Depression UK
- Hope2Sleep
- Maternal OCD
- Mind
- Mental health alliance
- Mental health foundation
- Mental health for self help and the big life group
- No panic
- Norther Ireland agoraphobia and anxiety society (NIAAS)

- OCD-UK
- OCD action
- PADNAS foundation
- Social anxiety UK (SA-UK)
- The sleep council
- Triumph over phobia

NICE National Institute for Health and Care Excellence

Adoption report: MT477 Alpha-Stim AID for Anxiety

Summary – MTAC1

Adoption levers

- Easy to use after basic training
- Safe and generally well tolerated with positive patient responses
- Provides a reportedly unmet need for non-pharmaceutical treatment options for anxiety, especially when there are long waits for CBT.
- Increases patient choice and may promote self-help and ownership of condition and treatment.
- When used as a stand-alone treatment it removes risks associated with antidepressant medication and unnecessary travel for CBT.
- May help patients with anxiety related to long-term conditions
- Easily disinfected device that can be delivered remotely

Adoption barriers

- Longer term treatment effects and need for repeat treatment unclear
- Potential for inconsistency and inequality in patient selection especially if demand exceeds supply
- Patients may sometimes need advice and support during treatment (time cost) but can be reduced with good training and information
- Concern that the device may be difficult to keep track of or may not be returned
- Potential clinician scepticism around the credibility of micro-currents
- Potential patient uncertainty around CES and how it can affect the brain.
- Battery powered only

1 Introduction

The adoption team aimed to collate information from healthcare professionals working within NHS organisations, who have experience of using Alpha-Stim AID.

However, there were no current routine NHS users of this product and therefore the information contained in this report represents the views of those who have used as part of research evaluations and of potential users only.

This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

2 Contributors

The adoption team spoke to 7 individuals including 6 NHS clinicians; a GP, a physiotherapist, a consultant psychiatrist and senior and research evaluation fellow (with research experience of using the device), an assistant director of mental health, a mental health quality lead and a GP with no experience of using the device.

One of the contributors is also the lead author on one of the studies included in the evidence review.

3 Use of Alpha-Stim AID in practice

Alpha-Stim AID is not currently being used in routine NHS practice. The company report that 156 devices were purchased in 2017 and were used in IAPT services until this was stopped by IAPT England because it was not a talking therapy. Three contributors are using it in two ongoing anxiety-related research studies.

All users recommended daily use for 6-8 weeks. The company state that 8 weeks is long enough to see if it is helping anxiety levels.

4 Reported benefits

The potential benefits of adopting Alpha-Stim AID as reported to the adoption team by the healthcare professionals using the technology are:

- Good option for people who do not want to take medication
- Good option for people who are on a waiting list for CBT (individual or group)
- Another treatment option (more treatment options were reportedly needed) that increases patient choice.
- Encourages self-management and people taking ownership of their condition and treatment
- Can be life changing for some people

5 Insights from the NHS

Area of application in NHS

The company state the device can be offered to patients in primary or secondary care (inpatients, community patients or outpatients).

All contributors said primary care (GP) or Improving Access to Psychological Therapies (IAPT) services would be the ideal setting for use. IAPT services are available country-wide but there is variation in services and treatments provided. One user said there were growing waiting lists for CBT within IAPT services and Alpha-Stim AID could be targeted at these patients.

In primary care, one user said while the GP would assess patient need, it could be a support worker or nurse who is trained to train the patient on its use.

One user said that hospital inpatients would be more severely unwell and that it would have limited use in this setting. A second user agreed having tried on 1 inpatient. The users also said it had potential value with other mental health conditions such as depression and bipolar disorder who may (or may not) also have anxiety and in people with anxiety associated with long term conditions such as COPD, MS or people taking multiple medications.

Care pathway

People with an anxiety condition usually visit their GP in the first instance. They can also self-refer (or be referred via their GP) into IAPT services where they can access treatment. There would be no change to the care pathway if Alpha-Stim AID were available as a stand-alone therapy or as an adjunct alongside other treatments. All users said there was no need for additional follow-up for patients using Alpha-Stim AID, although one did follow-up after 2 weeks under study conditions and another said that patients can sometimes need reassurance and support with its use. Good explanations and patient information may minimise this. Dissemination and retrieval of the device, decontamination and training patients were additional tasks associated with its use (see maintenance and training below).

Patient selection and equality

As there are several specific anxiety disorders, there are many potentially eligible people requiring step 3 level interventions.

Users said ideal candidates were people who reject medication, are looking for alternatives to medication or CBT or on a CBT waiting list.

The device was reportedly suitable for use in older people as well as with people with long term conditions (such as COPD and MS or people taking multiple medications), as long as the individual had good dexterity and could remember to use it, or had carer assistance. No reason why it could not be used in children was reported. People with cochlear implants must have the type that can be switched off.
The exclusion criteria listed by the users were:

- seizures
- pacemakers/implanted devices (e.g. defibrillators)
- pregnancy (FDA requirement although safety aspect is being explored)

When offering Alpha-Stim AID to patients, supply of machines needs to meet the demand. Depending on patient throughput and eligibility this could mean many machines would need to be available at any one time (at additional capital outlay) to ensure equitable patient selection. If not, this could lead to clinicians selecting/deselecting patients based on perceptions around suitability, ability to self-operate, patients' social circumstances/lifestyle or symptoms associated with other co-morbidities.

Clinician confidence/acceptance

The users had confidence in the scientific plausibility behind cranial-electrical stimulation and said that more non-pharmacological, self-help treatments for anxiety were needed to increase patient choice. They liked the self-help aspect as patients can take ownership of their condition and treatment.

Several contributors (both users and non-users) were keen to understand if the anxiety reducing effects could be maintained over time and if there was evidence to demonstrate this. If so, they said this would be the biggest lever to its adoption. If not,

a non-user queried whether patients would require periodic treatment and the impact of this on machine availability and numbers needed.

One non-user was unfamiliar with CES, the credibility of micro-currents and their effect on the brain and said patients may also be dubious or fearful or even confuse it with electroconvulsive therapy. He said good quality clinician and patient information could help allay these concerns.

Patient experience

The users agreed that the device is portable, light and non-burdensome for patients.

The users reported positive feedback from several patients who had used the device. One user had 2 patients who reported it did not work for them and returned the machine early. A few patients reported they did not think it was working while on a low level because it was inaudible. Patient reassurance is important here (it is subsensory at low level but checking the digital display confirms whether it is working). Support and encouragement to complete the treatment cycle could also be reiterated.

One user experienced low uptake (1/7) of patients opting for this treatment in a research setting and felt this was because it was unexpected and unfamiliar, and patients may have been concerned it would affect their place on the waiting list for CBT. Going forward, he felt more detailed explanations and patient information, as well as clinician reassurance about list position would help uptake.

One user described a patient who had been extremely anxious with COPD and had a husband who was unwell in hospital. This user described the effect of alpha-stim AID as ‘life-changing’ for this patient as she was suddenly much calmer and able to cope with her condition and with her husband’s subsequent death.

One user had experienced patient refusal because they felt they could not spare an hour in the day when they could attach themselves to the machine and still manage the other demands on them. One of the non-users also perceived this as a potential challenge. The company instructions state that it is best to relax during treatment. If time is a factor, one user suggested using on a higher setting for a shorter duration although side effects may be more likely (see patient safety).

Patient safety

The four users said Alpha-Stim AID was safe and generally well tolerated by patients. A small number of patients who used at a high setting experienced minor side effects such as nausea, headache or dizziness. It is possible to lock the machine at a low level prior to disseminating. It is also possible to pre-set treatment duration for auto cut off, to prevent any such ill effects.

One user reported that a few patients blamed the machine for unusual symptoms which he felt were unrelated to the machine and more related to their condition.

Another user reported that using Alpha-Stim AID as a stand-alone treatment in place of antidepressant medication avoided the safety risks and risks of dependency associated with these.

The instructions state the device should not be used while driving or operating dangerous tools or machinery.

Commissioning and procurement

Commissioning arrangements will depend on setting of use. In IAPT services commissioning decisions can be aided by local pilot work whereby opportunities for cost avoidance are obtained. There are multiple contractual arrangements which could be utilised in IAPT services which would be subject to CCG determination. One option would be to include Alpha-Stim AID within the CCG block contract where the IAPT service would be responsible for purchasing and managing its use. Alternatively, the CCG could contract directly with the provider specifying conditions and maintaining oversight of its use. Each option could allow for bulk order discounts.

If used at the GP practice level, one GP user felt purchasing decisions should be at the Primary Care Network level, however this could introduce local variation if commissioning is not consistent across a STP/ICS.

Training and compliance

The users report the device is easy to use and minimum training is required. Full instructions are included in the device pack. There were no issues reported around

training patients how to use at home. All users said compliance was good, but it was important patients had good dexterity and could remember to use the device or they had adequate carer support. Because of the COVID-19 pandemic, where anxiety treatment demands are reportedly increased, training could be delivered remotely providing patients have adequate technology to support this.

Maintenance/quality control

The company advise Alpha-Stim AID has a 5-year warranty and no servicing is required. They state any faulty devices (within that time) will be replaced for free via the care provider. Two AAA 1.5volt batteries are required to power the device. The device comes with two batteries and two spares should be provided.

One user reported that a patient stopped using the device believing it was faulty, but the batteries were flat. Advising patients about the batteries in advance and reminding them of the battery life indicator on the screen was thus reported to be important. One potential user reported a rechargeable device would be preferable to battery operated.

The company advise the ear pads should be changed approximately weekly or when they are soiled and always from one patient to another. The ear clips should be cleaned with an alcohol wipe after use and prior to re-issue. One user has developed a SOP for cleaning. Complete disinfection of the device is vital owing to the COVID-19 pandemic. Patients may need reassurance that this has taken place to demonstrate safety and facilitate acceptance.

Misuse and safe return of the devise by the patient was a concern raised by the potential users however the users within study conditions found generally good patient compliance and return of equipment.

6 Comparators

No other CES devices were mentioned.

raNATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT477 Alpha Stim AID for Anxiety

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Electromedical Products International, Inc.
Submission date	April 28, 2020
Regulatory documents attached	Instructions for use CE Certificate
Contains confidential information	Yes

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with anxiety disorders.	People with anxiety symptoms but have not yet been diagnosed for anxiety disorders.	Published evidence to support the use of the device in this group of the population, presented below.
Intervention	Alpha-Stim AID	Enter text.	Enter text.
Comparator(s)	Pharmacological interventions (e.g. selective serotonin reuptake inhibitors) Psychological interventions (e.g. group or individual CBT)	Enter text.	Enter text.
Outcomes	The outcome measures to consider include: • Anxiety and depression symptoms scores • Social and occupational functioning • Quality of life • Use of psychological interventions • Use of pharmacological interventions • Number of GP visits • Waiting time for psychological treatments • Pharmacological related adverse events such as overdose	Enter text.	Enter text.

	• Patient quality of life measures • 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 long enough to reflect 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 of combinations of devices are needed.	Enter text.	Enter text.
Subgroups to be considered	• People who also have other mental health disorders such as depression • People with other comorbidities (i.e. chronic conditions) • Severity of anxiety	Enter text.	Enter text.
Special considerations, including issues related to equality	The condition can have a significant effect on individuals' daily lives. This may mean someone disabled in their anxiety disorder has a substantial and long-term effect on their ability to do daily activities. Disability is a protected characteristic under the Equality Act.	Enter text.	Enter text.

	People from certain socially excluded groups that would benefit from psychological interventions might be less likely to access them, such as black and minority ethnic groups; older people; people unable to leave their homes, including those shielding from COVID-19, anxiety-related fears, or chronic disabilities; those in prison or in contact with the criminal justice system; and ex-service personnel. Young women are more likely to have anxiety disorder. Sex and age are all protected characteristics under the Equality Act 2010.		

2 The technology

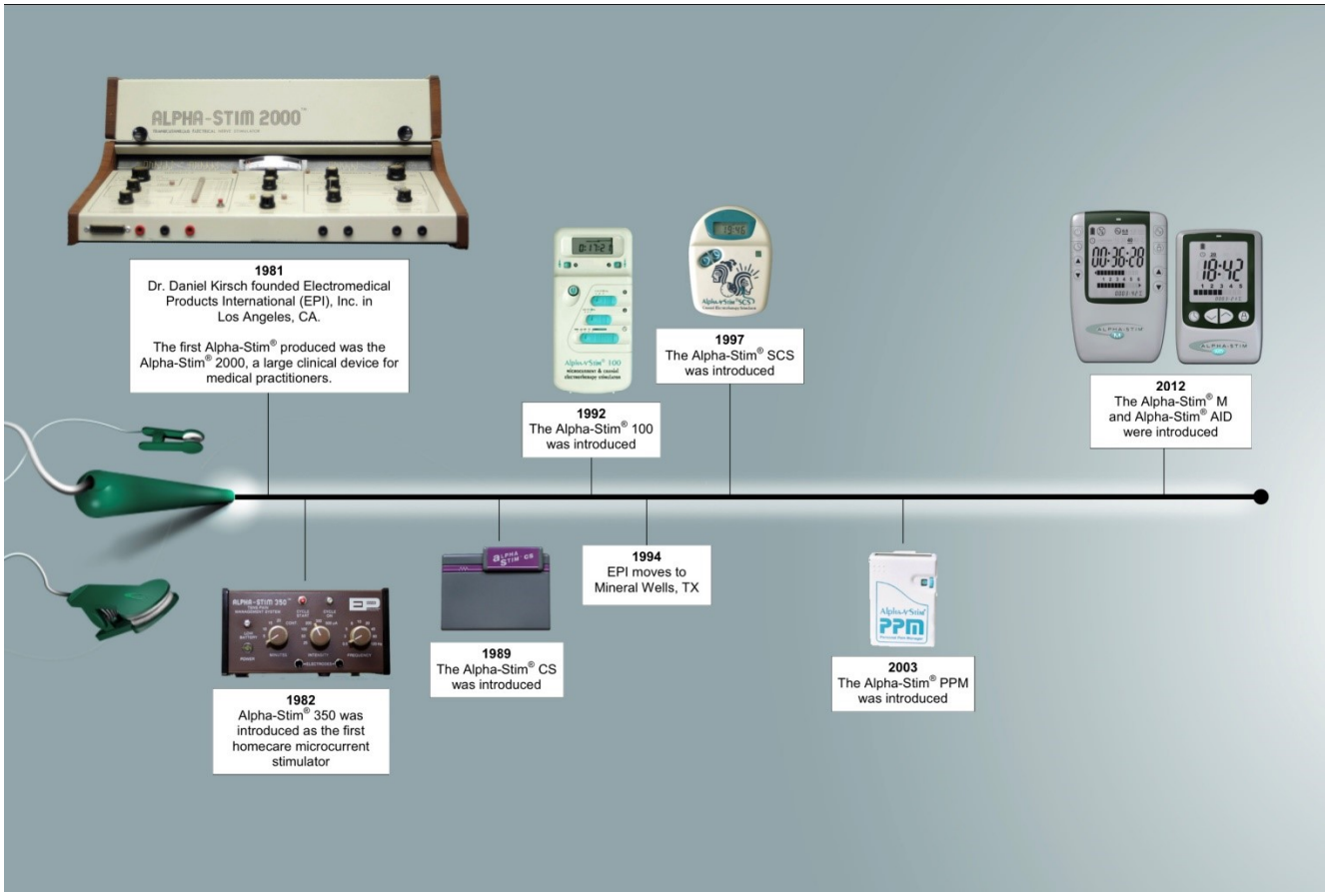
Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Alpha-Stim
Approved name	Alpha-Stim
CE mark class and date of authorisation	Class IIa Most recent authorization date 29 April, 2019

The table below summarizes, in reverse chronological order, the different versions of Alpha-Stim devices. All versions of Alpha-Stim utilize the same patented waveform and mechanisms. However, presentations of each device and features regarding patient

interface (such as buttons instead of knobs and larger LCD display) are incorporated into newer generations of the device.

Version(s)	Launched	Features
Alpha-Stim AID	October 2012	One Channel cranial electrotherapy stimulator. The frequency is 0.5Hz with a maximum current output of 500 microamperes. Output is patient controlled and ranges from 50 to 500 microamperes.
Alpha-Stim M	October 2012	Two Channel cranial electrotherapy stimulator and microcurrent electrical therapy stimulator. The frequencies are 0.5 Hz, 1.5 Hz, or 100 Hz and can be set by the patient. Maximum current output is 600 microamperes. Output is patient controlled and ranges from 50 to 600 microamperes.
Alpha-Stim PPM	2003	Two Channel microcurrent electrical therapy (MET) stimulator. The frequency is 0.5Hz with a maximum current output of 500 microamperes. Output is patient controlled and ranges from 50 to 500 microamperes.
Alpha-Stim SCS	1997	One Channel cranial electrotherapy stimulator. The frequency is 0.5Hz with a maximum current output of 500 microamperes. Output is patient controlled and ranges from 10 to 500 microamperes.
Alpha-Stim 100	1992	Two Channel cranial electrotherapy stimulator and microcurrent electrical therapy stimulator. The frequency is 0.5Hz with a maximum current output of 600 microamperes. Output is patient controlled and ranges from 10 to 600 microamperes.
Alpha-Stim CS	1989	Two Channel cranial electrotherapy stimulator and microcurrent electrical therapy stimulator. The frequency is 0.5Hz with a maximum current output of 600 microamperes. Output is patient controlled and ranges from 10 to 600 microamperes.
Alpha-Stim 350	1982	One Channel cranial electrotherapy stimulator. The frequency is 0.5Hz with a maximum current output of 500 microamperes. Output is patient controlled and ranges from 25 to 500 microamperes.
Alpha-Stim 2000	1981	Three channels total, one channel exclusive for cranial electrotherapy stimulation. The frequency is 0.5Hz with a maximum current output of 500 microamperes. Output is customer controlled and ranges from 0 to 500 microamperes.



What are the claimed benefits of using the technology for patients and the NHS?

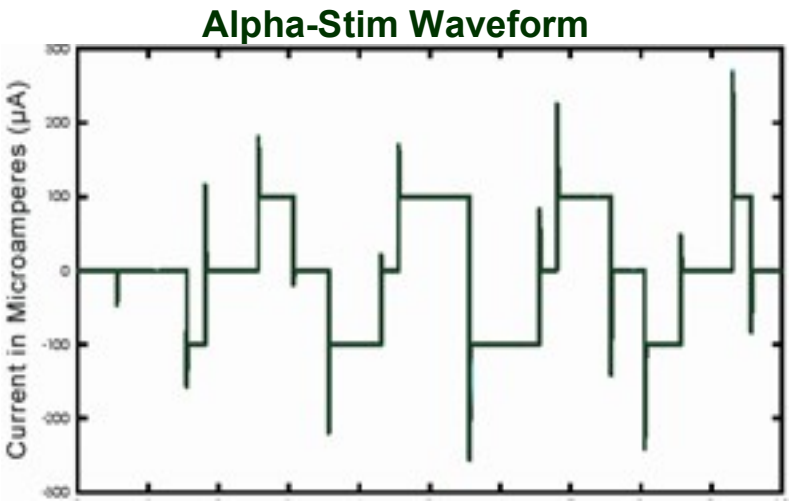
Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Reduction in anxiety symptoms	Meta-analysis, RCTs, open label studies, also studies of cancer, pain, functional constipation, and other mental disorders including PTSD, depression symptoms.	Decades of clinical research, as discussed below, have demonstrated the effectiveness of Alpha-Stim in reducing anxiety symptoms for a wide variety of patient populations and comorbid conditions.
Reduced reliance on medications.	The clinical evidence outlined below (i.e., Morriss et al., 2019; Morrow et al., 2019, Lu & Hu, 2014) indicates the safety and effectiveness of Alpha-Stim as a stand-alone treatment for anxiety as an alternative to medications, or as an adjunct treatment to increase the effectiveness of medications.	Alpha-Stim is demonstrated as a safe and effective treatment option for anxiety, thus reducing the need for medications, which have more adverse effects than Alpha-Stim.
System benefits		
Reduced need for Cognitive-Behavioral Therapy (CBT).	As discussed in Morriss et al. (2019) below, Alpha-Stim effectively decreased anxiety and thus reduced the need for patients to have CBT.	Reducing anxiety, and thus need for patients to have CBT, allows more patients to be treated by IAPT or by primary care and secondary care services without needing IAPT. The result is greater throughput of patients receiving effective treatment for anxiety at little or no additional cost.

Improved treatment in subgroups where additional medication is contraindicated.	As stated above, clinical evidence presented below demonstrates the effectiveness and safety of using Alpha-Stim as a stand-alone treatment for anxiety.	Alpha-Stim has been utilized to treat anxiety, both in research and in clinical practice, with a wide variety of populations and comorbid conditions with no serious adverse effects.
Cost benefits		
Reduced cost for treatment of anxiety compared to current pathway.	As discussed in Morriss (2019) below, treating anxiety with Alpha-Stim resulted in a savings of £540 or more per patient.	Similar cost to antidepressants and lower than high intensity psychological treatment if used after watchful waiting and low intensity psychological interventions in NICE GAD pathway.
Sustainability benefits		
Patients can re-use Alpha-Stim devices in their homes.	The clinical evidence below indicates participants were able to utilize the same Alpha-Stim device repeatedly during each study.	Ease of use for primary care and secondary care and, once adequate mental health assessment has been made by a qualified health professional, easily implemented through support staff or even directly through distributor as are devices for other conditions ranging from diabetes self-monitoring and treatment, TENS devices for pain etc. Alpha-Stim can be a high volume intervention using minimal consumption of skilled health professional time plus established track record of distribution should ensure sustainability.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The Alpha-Stim® cranial electrotherapy stimulator is a neurological medical device that uses low level electrical signals, delivering a current of 100 to 600 microamperes (μA), at a frequency of 0.5 Hz, applied transcranially for the treatment of anxiety, insomnia, depression and pain. The device consists of an electrical pulse generator which is operated by 2 1.5-volt batteries, patient-connect hardware which consists of ear clip electrodes, and an electroconductive solution for moistening the electrodes to assure good electrical contact through the skin. The device is accompanied by an owner's manual that provides directions for use and warnings against unsafe use. Alpha-Stim® CES treatment has been available in doctor's offices, clinics, and hospitals, and for home use upon an order from a licensed health care provider, in the United States since 1981. It is sold over the counter (without a prescription) worldwide except in the USA and Canada. When properly used in accordance with the instructions, Alpha-Stim® CES devices are safe, effective, and simple to use.

Alpha-Stim® technology uses a complex and patented bipolar asymmetric waveform consisting of multiple frequencies at a 50% duty cycle having a maximum pulse width of 0.5 Hz (2 seconds) provided over a ten second time frame with random factors to avoid habituation by the nervous system. The maximum current level is 600 microamperes. The impedance range within which the waveform parameters remain valid is from 100 Ω to 10 K Ω. It is balanced to achieve 0 net current in either direction as shown in the waveform graphic below. The waveform is patented. (US patent No. 8612008, Europe, China, Russian and other patents have been issued or are pending). Used in 8 generations of Alpha-Stim® products since 1981, the unique Alpha-Stim® technology has been proven consistently effective in many randomized double-blind sham-controlled studies and has been used safely by millions of people worldwide. Through the alteration of brain physics (brainwave electrical activities) and brain chemistry (neurotransmitters), research has shown that CES can significantly decrease anxiety, insomnia, depression and pain when used at a medical clinic or at home by the patient. In 39 years of use, there have never been any significant side effects reported.



The Alpha-Stim® waveform shown over a ten second time period.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Alpha-Stim® technology is durable medical equipment electrical stimulator with a 5-year warranty period. The device is reusable. Its accessories are patient specific and must be discarded at varying intervals as outlined in the instructions for use accompanying each device.

When the end-user wishes to discard this product which contains plastics and electronics, it must be sent to separate collection facilities for recovery and recycling. By separating this product from other household-type waste, the volume of waste sent to incinerators or land-fills will be reduced and natural resources will thus be conserved.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

Primary care GP Services

Patient consults GP (or prescribing nurse) face to face or remotely who assesses the patient for anxiety.

↓

GP diagnoses Generalised Anxiety Disorder with GAD-7 score ≥10, has functional impairment at step 3 of NICE GAD pathway, offers Alpha-Stim CES as alternative to drug treatment and high intensity psychological treatment after steps 1 and 2 of NICE GAD pathway (step 1, education and watchful waiting 2 weeks, step 2 low intensity psychological intervention offered and not effective or refused by patient).

↓

Practice nurse or health care assistant or direct from company (during covid-19) supplies Alpha-Stim CES and shows how to use (covid-19 telephone call and video presentation)

↓

Daily use by patient at home for 60 minutes for 6 weeks

↓

Telephone support within 72 hours

↓

Practice nurse, health care assistant or company collects Alpha-Stim CES. Completes GAD-7. Signposts to GP if GAD-7 score ≥10 and functional impairment for drug or high intensity psychological treatment. (In consultation with GP offers further 6 weeks Alpha-Stim CES if partial response e.g. 25-50% drop in score and ≥8 on GAD-7)

Primary Care Improving Access to Psychological Treatment (IAPT)

Self-referral or primary care referral.

↓

Generalised Anxiety Disorder diagnosed. Low intensity psychological intervention given. GAD-7≥8 because this is the current IAPT threshold to be offered high intensity psychological treatment. Eligible for high intensity psychological intervention, either on waiting list for high intensity psychological treatment or prefers to have Alpha-Stim CES.

↓

IAPT Psychological Wellbeing Practitioner (PWP) shows how to use Alpha-Stim CES and supplies for 6 weeks

↓

Telephone support within 72 hours

↓

IAPT PWP collects Alpha-Stim CES. Completes GAD-7. If GAD-7 ≥8 offered high intensity treatment if on waiting list for it already or offered high intensity if not or discharge to GP (offers further 6 weeks Alpha-Stim CES if partial response on GAD-7)

Secondary care mental health or long-term conditions pathway

Existing patient with serious mental illness or long-term physical condition diagnosed with comorbid Generalised Anxiety Disorder that is impairing function and GAD-7 ≥10 that has not improved with education and simple psychological intervention. Additional medication undesirable e.g. sedation, addiction potential or contraindicated.

Mental health professional or support worker shows how to use Alpha-Stim CES and supplies for 6 weeks

Telephone support within 72 hours

Mental health professional or support worker collects Alpha-Stim CES. Completes GAD-7. Consider high intensity psychological treatment if GAD-7 score >10 and functional impairment. (In consultation with mental health professional offers further 6 weeks Alpha-Stim CES if partial response e.g. 25-50% drop in score and >8 on GAD-7)

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

Alpha-Stim CES has been designed to be easy to use and most people can use it by following written instructions provided with the equipment. The instructions for use, as well as animated treatment procedures and protocols are also available online at https://www.alpha-stim.com/training/. Weekly certification webinars for licensed healthcare professionals are also available and can be enrolled in at https://www.alpha-stim.com/educational-opportunities/. Health professionals may also request a brief individual training (maximum 30 minutes) on how to use it, in whom is suitable and contraindicated, and on commonly encountered frequent questions that users of the device with anxiety may have.

Patients will require 10-15 minutes training on how to use the device when they first receive it. Patient and public involvement representatives including patients who have used the device but not exclusively, advise that a telephone call within 72 hours of receiving the device is useful both to address any questions the participant may have and as a motivational aid to use the device daily.

The use of Alpha-Stim CES device is similar to other devices and equipment supplied to patients so primary care and secondary care organisations managing long-term conditions will easily accommodate the use of this device. Pilot studies have shown that Improving Access to Psychological Treatment Services will require little change in their system of care because Alpha-Stim CES could be offered at the assessment of progress after the low intensity intervention.

Secondary care mental health services do not routinely provide devices in their care pathway but these could easily be organised at a community mental health team base through support workers or nurses. Most mental health services clinics are organised to provide depot antipsychotic medication so the provision of Alpha-Stim CES devices might be an extension of clinic provision.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		35
Number of studies identified as being relevant to the decision problem.		24
Of the relevant studies identified:	Number of published studies (included in table 1).	21
	Number of abstracts (included in table 2).	1
	Number of ongoing or unpublished studies (included in table 3).	2

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

The following studies are presented as key evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Journal of Affective Disorders, 250(2019), 426-37	Morriss et al., 2019 Two NHS Improving Access to Psychological Treatment (IAPT) services in the same county in England.	Open Label	161 patients with diagnosis of GAD on waiting list for individual Cognitive Behavioral Therapy 49 participants withdrew by week 12: 9 could not find the time to complete the treatment, 4 withdrew because of no improvement, 4 participants withdrew due to reported side effects; headache (N=2), nausea (N=1) and “strange feeling” (N=1), 2 withdrew because they felt better, and 30 gave no reason. 81 participants completed follow ups to 12 weeks and 72 completed follow ups to 24 weeks.	Alpha-Stim for 60 minutes a day, 7 days a week, for six consecutive weeks.	N/A	The primary outcome is the proportion of participants who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7. 72 (44.7%) and 77 (47.8%) achieved remission on the GAD-7 at 12 and 24 weeks respectively with 122 (75.8%) receiving at least 6 weeks CES. Mean (SD) GAD-7 score at baseline significantly improved from 15.77 (3.21) to 8.92 (5.42) and 8.99 (6.18) at 12 and 24 weeks respectively ($p<0.001$). 80 (49.7%) participants required further individual CBT.

Journal of Depression and Anxiety, 8(2)	Kirsch TB, et al., 2019 Mineral Wells, Texas Independent School District	Open Label	35 teachers working for the school district using Alpha-Stim devices at home and recording results with a smartphone app. No participants withdrew from the study.	Alpha-Stim use for 20-60 minutes daily for six weeks.	N/A	Monitoring Alpha-Stim CES treatment using a 0-10 Numerical Rating Scale (NRS) on a smartphone app. Outcome measures were anxiety, depression, insomnia and pain. Anxiety scores reduced from a mean of 6.13 (2.4) at baseline to 1.26 (0.89) at posttest ($p<0.001$). This treatment effect with Alpha-Stim CES on anxiety, insomnia, depression, and pain was consistent with prior surveys and confirmed the precision of the new app in determining progress from a single treatment and a series of treatments.
Federal Practitioner, 36(4), 181-7	Morrow et al. (2019) Eastern Oklahoma VA Health Care	Open Label	161 veterans in the EOVAHCS Pain Modality Clinic,	For Alpha-Stim, veterans came to the clinic 5 days a week for two	N/A	The Beck Depression Inventory (BDI), The Beck Anxiety

	System (EOVAHCS) Pain Modality Clinic, Muskogee, Oklahoma, USA		reporting anxiety comorbid with pain. 46 participants failed to complete a trial due to travel barriers, lack of interest in continuing, and for 3 veterans, reports of headaches that they attributed to the Alpha-Stim treatment. Of the remaining 115 participants, 50 completed trials with the Alpha-Stim and 38 completed trials with a Laser Touch One (LTO) device. No participants completed trials with both devices.	weeks. For LTO, veterans came to the clinic 5 days a week for one week.		Inventory (BAI), The Pain Catastrophizing Scale (PCS), The Subjective Units of Distress Scale (SUD), The Brief Pain Inventory (BPI). SUD score means decreased from 6.23 (preintervention) to 3.51 (postintervention) ($p<0.01$). Anxiety (as measured by the BAI) was significantly reduced from a preintervention mean of 20.07 to a postintervention mean of 11.96 ($p<0.01$). In addition, veterans completing Alpha-Stim treatment showed a statistically significant improvement in self-reported relaxation scores.

Journal of Pain and Symptom Management, 55(2), 198-206	Yennurajalingam, 2018. MD Anderson Cancer Center in Houston, Texas, USA	Open Label	36 patients with diagnosis of advanced cancer and one or more of the four symptoms (depression, anxiety, sleep disturbance, and pain) on palliative care. 52 patients were initially enrolled. 1 was removed for noncompliance to study protocol, 2 no longer wished to participate due to disease progression, 16 signed consent but did not participate in study procedures or baseline assessments.	Alpha-Stim treatment 60 minutes daily for four weeks.	N/A	Edmonton Symptom Assessment (ESAS), Hospital Anxiety and Depression Scale (HADS); 33/36 (92%) completed the CES. Median (IQR) adherence CES use and satisfaction scores were 93% (89-100) and 10 (9-10) respectively and the adherence criteria was met in the study. Participants demonstrated significant improvement in anxiety symptoms and severity, as measured by the HADS (p=0.024) and the ESAS (p= 0.001) during 4 weeks of CES treatment.
Journal of Neurogastroenterology and Motility, 22(3), 497-508	Gong et al. (2016). Tianjin, China	Open Label	74 patients with functional constipation (FC) who visited the	Control group participated in biofeedback therapy (BFT).	N/A	Self-Rating Anxiety Score (SAS): After treatment, the participants in the

			Pelvic Floor Center Nankai University Affiliated Hospital between April 2014 and March 2015. No patients withdrew or were removed from the study.	The Experimental group participated in CES with BFT.		experiment group had significantly lower anxiety, as measured by the SAS ($p<0.001$), than the control group. The experimental group also had significantly lower scores in depression and Wexner constipation score than the control group (all $p< 0.05$). The number of successful expulsions in the experiment group was larger than the control group ($p= 0.016$).
Energy Psychology, 7(2), 33-44	Libretto et al. (2015). Fort Hood, Texas, USA.	Retrospective	764 active-duty soldiers participating in The Warrior Combat Stress Reset Program (Reset) from August 2008 to September 2015. As this was a retrospective study,	Alpha-Stim CES treatment as part of a multi-modal, multiphase, intensive day-treatment program.	N/A	Beck Anxiety Inventory. This retrospective case series evaluated the efficacy of the Fort Hood Combat Stress Reset program. Anxiety was measured using the BAI at day 1 and at 3 weeks. From 2008 to 2013

			no participants withdrew or were removed from the study.			the mean initial score went from 27.0 to 20.9 (-6.3, p<0.0001).
Journal of Affective Disorders, 164, 171-7	Barclay & Barclay (2014). Liberty University, Virginia, USA.	Double-blind RCT	115 individuals ages 18 – 65 meeting criteria for an anxiety disorder. 115 participants began the study, 7 were lost to follow up before completing the study, 7 were excluded from analysis due to not completing scheduled data collection.	Alpha-Stim CES treatment 60 minutes daily for 5 weeks	Placebo control and experimental groups. Devices for experimental group were locked at 100 μA for 60 minutes. Devices for the control group were set to look the same as active devices, but emit no current.	Hamilton Rating Scale for Anxiety (HAM-A): In the active treatment group, 83% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-A (p<0.001). There was a significant difference between groups (p<0.001, *d*=0.94) from baseline to endpoint of study. The mean decrease on the HAM-A in the treatment group of 32.8% (19.89 to 13.37) was more than 3 times the mean decrease on the HAM-A for the sham group of 9.1% (21.98 to 19.98) from baseline to endpoint of the study. Hamilton Depression Rating Scale (HAM-D_{17}): In the active

						treatment group, 82% had a decrease of ≥ 50% in scores from baseline to endpoint on the HAM-D17 ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.78$) on the HAM-D17 from baseline to endpoint of study. The mean decrease on the HAM-D17 in the treatment group of 32.9% (9.64 to 6.47) was more than twelve (12) times the mean decrease on the HAM-D17 for the sham group of 2.6% (10.22 to 9.96) from baseline to endpoint of study.
The Army Medical Department Journal. October-December 2014, 46-54.	Kirsch et al. (2014). Postmarketing survey in the United States.	Survey	145 veterans and service members who had been issued Alpha-Stim devices through VA or DoD medical centers.	Survey respondents were using Alpha-Stim as needed to treat their anxiety disorders.	N/A	Over 60% of respondents indicated CES treatment resulted in considerable or marked improvement in their anxiety or PTSD symptoms. Of the respondents using Alpha-Stim as

						a stand-alone treatment (no medications) for PTSD and anxiety, over 50% reported considerable or marked improvement in their symptoms. 99% of respondents indicated CES treatment was safe.
Medical Innovation of China, 11(08), 080-2	Lu & Hu (2014). China	RCT	120 patients being treated, either as inpatient or outpatient, for anxiety disorders in a hospital in China. No participants withdrew or were removed from the study.	Alpha-Stim treatment for 60 minutes daily for 6 weeks.	The two groups in this study were Paxil only (control) and Paxil plus CES (treatment).	In the CES study group, 18 cases were cured, 28 cases were obviously improved, 10 cases were improved, and 4 cases were ineffective. Therefore, the significant efficacy rate was 76.67%. In the control group, the corresponding significant efficacy rate 53.33%.
Journal of International Medical Research, 41, 1788-95	Lee et al. (2013). Department of Anesthesiology and Pain Medicine, Ansan Hospital of Korea University College of Medicine	Double-blind RCT	50 female patients aged 20-65 awaiting thyroidectomy for suspected thyroid cancer. No participants withdrew or were removed from the study.	20-minute CES treatment on the day before and the day of surgery.	Treatment group received active CES treatment. Control group had identical devices, but no current was provided.	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale than the control group, which had usual care (p=0.016). There was also a

						reduction in withdrawal scores for patients during injections (p=0.049).
ISOR Journal of Dental and Medical Sciences, 10(4), 51-7	Koleoso et al. (2013). Dental Centre of University of Benin Teaching Hospital, Benin City, Nigeria	RCT	40 dental patients with facial pain scoring high in dental anxiety on the Modified DAS.	3 days of treatment. Participants in CES groups received 45 minutes of CES treatment each day. Participants in relaxation groups listened to music from an MP3 player via earphone for 30 minutes each day.	One control group and three treatment groups (relaxation only, CES only, relaxation + CES).	Modified Dental Anxiety Scale (MDAS) The CES group (posttest Means=10.20), the relaxation group (M=10.70) and the combined treatment group (M=9.40) had significantly lower anxiety (p<0.01) than the control group (M=18.30). Each of the 3 treatment groups significantly decreased dental anxiety (p<0.05) from pre-test to post-test. There was no statistically significant difference among the 3 active treatment groups on dental anxiety.
Korean Journal of Anesthesiology, 55, 657-661	Kim et al. (2008). Korea University College of Medicine	RCT	60 patients between the ages of 18-65 awaiting surgery under general anesthesia. No participants	20-minute CES treatment in the operating room waiting area.	Active and control groups. Control group did not receive CES treatment.	CES group had significantly lower scores from baseline on Likert anxiety scale than control group at end

			withdrew or were removed from the study.			point of study (p< 0.05, *d*=-.88).
Journal of Clinical Rheumatology, *7*(2), 72-8	Lichtbroun et al. (2001). Robert Wood Johnson Medical School, East Brunswick, New Jersey, USA	Double-blind RCT with an open-label extension phase	60 patients diagnosed with and receiving treatment for fibromyalgia. No participants withdrew or were removed from the study.	Alpha-Stim CES for 60 minutes daily for three weeks.	Treatment group received active CES treatment. Sham group had identical devices, but no current was provided. Placebo control group was on a wait list for CES treatment. At the end of the initial three-week period, the groups were unblinded, and participants in the sham and control groups were given the opportunity for three weeks of active CES treatment.	Profile of Mood (POMS):The active CES group had significant findings on 8 of the 11 variables compared to the sham group: significantly lower anxiety scores (p=0.04, d=-.60), higher quality of sleep scores (p=0.02, d=.45), lower pain scores (p=.004, d=.65), higher feelings of well-being scores (p=.007, d=.73), higher quality of life scores (p=.001, d=.97), lower fatigue scores (p=0.03, d=-.72 and lower anger scores (p=0.04, d=.60) compared to sham group.
General Dentistry, 47(1), 50-5	Winick (1999). TMD and Facial Pain Clinic, New York Eye and Ear Infirmary, New York City, NY, USA	Double-blind RCT	33 dental patients with anxiety. No participants withdrew or were removed from the study.	CES treatment starting 5 minutes before and lasting until the end of the dental procedure.	Active group received active CES treatment. Placebo group had identical devices,	Visual Analogue Scale: The active CES groups had lower anxiety scores (VAS) from baseline to endpoint of the study than the sham group as

					but no current was provided.	measured by the dentist investigator (p<.02) and subjects (p<.02). Findings using an inverse Likert scale corroborated these findings for both the investigator evaluation (p<.01) and subjects' evaluation (p<.01).
American Journal of Electromedicine, 16(1), 49-51	Overcash (1999). Private practice mental health clinic in Chambersburg, PA	Open Label Retrospective analysis	197 patients being treated for acute anxiety disorders between January 1989 and January 1995. 15 patients failed to complete treatment and were not included in study results.	Alpha-Stim CES treatment once or twice daily.	N/A	Subjects had significantly lower scores on the 0-100 numerical rating scale for anxiety (p<.05), significantly lower EMG scores (p<.05), significantly lower EDR scores (p<.05) and significantly higher finger temperature scores (p<.05) at post-test from baseline, with all factors indicating and cross confirming less anxiety.
American Journal of Electromedicine, 4(1), 18-21	Gibson & O'Hair (1987). California College of Professional Psychology, San	RCT	64 volunteers responding to a newspaper ad and scoring 50 or higher on the State-Trait Anxiety Inventory.	A single 20-minute treatment session with either relaxation instructions, CES treatment, both, or	Participants were randomly divided into four groups: a control group receiving no treatment, a	Subjects responded on the STAI significantly (p<.001) better than controls and equally to either relaxation therapy alone with a

	Diego, California, USA		Nine participants were removed for either failure to meet study criteria or failure to show for treatment sessions.	listening to a neutral recording with no CES.	relaxation training only group, a CES treatment only group, or a combined relaxation training/CES group.	means of 52.88 pretest to 32.19 post, CES alone: 52.31 pre to 30.06 post, or both relaxation therapy and CES together: 53.69 pre to 30.44 post. The control group only dropped from 53.25 to 51.94.

The following studies are presented as supporting evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Jacobs Journal of Psychiatry and Behavioral Science, 6(1), 25-31	Platoni et al., 2019 Mineral Wells, Texas police and fire departments, the Palo Pinto County Sheriff's Department, and the Dayton, Ohio police department	Open Label	76 police officers from the 3 law enforcement agencies and 10 firefighters. No participants withdrew from the study.	Alpha-Stim use for 20-60 minutes daily at least 5 days per week for six weeks.	N/A	Monitoring Alpha-Stim CES treatment using a 0-10 Numerical Rating Scale (NRS) on a smartphone app. Outcome measures were anxiety, depression, Insomnia and pain. The anxiety pretest mean was 4.18 and posttest mean of 1.93 for a reduction of 54% ($p<.001$), and effect size $d=1.21$ (large). These 86 police officers, sheriff's officers, and firefighters experienced a very significant decrease in anxiety, insomnia, depression, and pain by using Alpha-Stim CES. The statistical analyses revealed highly

						significant values of p<.001 for anxiety, depression, insomnia, and pain. The effect size Cohen's d values were large for all outcome measures indicating a high level of practical change from baseline to posttest, which supports the capability of Alpha-Stim CES technology in reducing anxiety, insomnia, depression and pain symptoms and the ability to monitor progress on the Alpha-Stim app.
Primary Care Companion for CNS Disorders, 20(1)	Lande & Gragnani (2018). Walter Reed National Military Medical Center, Bethesda, Maryland, USA	Open Label	50 active duty service members receiving treatment at the Psychiatric Continuity Service, Walter Reed National Military Medical Center, an outpatient partial hospitalization	Alpha-Stim treatment once for 20 minutes	N/A	qEEG changes when comparing qEEG results pre- and post-CES treatment**.** Brain wave measurements taken immediately after the 20-minute CES session

			program. The typical participant was mildly depressed and had severe trauma-related symptoms and sleep problems. No participants withdrew or were removed from the study.			showed a significant and strong effect in the beta region, suggesting an increase in mental alertness, focus and concentration. Significant changes were seen as quickly as 10 minutes and the strong effect in the beta region persisted through the 10-minute follow up, indicating increased mental alertness. Participants also reported significant reduction in distress following the CES treatment. This finding may be related to the increase in beta wave activity. Improved mental focus and corresponding decrease in distraction may be a welcome relief

						among individuals with overlapping anxiety, depression and trauma symptoms as reflected in this study group.
The Correctional Psychologist, 41(1), 9-15.	Mellen & Mackey (2009). Rural Sheriff's jail in Alabama, USA.	Double-blind RCT	21 sheriff's officers using Alpha-Stim CES during the course of their job duties. One person withdrew from the study due to increased feelings of agitation.	20 sessions, each lasting 20 minutes.	Treatment group received active CES treatment. Control group had identical devices, but no current was provided.	Reductions in anxiety, as measured by the BAI and the BSI, were nonsignificant between the control and treatment group. However, a trend analysis indicates a positive change in overall psychological functioning, indicating that Alpha-Stim CES provides a global brain modulation, rather than the targeted approaches of psychotropic medications.
American Jails, *22*(5), 32-38	Mellen & Mackey (2008). Rural Sheriff's Jail, Alabama, USA	Double-blind RCT	22 sheriff's officers using Alpha-Stim CES during the course of their job	20 sessions, each lasting 20 minutes.	Treatment group received active CES treatment. Control group had	Significant changes were found in the treatment group's BSI results,

			duties. One person withdrew from the study due to increased feelings of agitation.		identical devices, but no current was provided.	suggesting a positive influence from using CES. In addition, the treatment group findings support the argument that Alpha-Stim CES provides a global brain modulation.
The Internet Journal of Anesthesiology, 8(2)	Cork et al. (2004). Department of Anesthesiology, Louisiana State University (LSU) Health Science Center, Shreveport, LA, USA	Double-blind RCT with open label extension phase	70 patients ages 22-75 presenting at the LSU Pain Clinic with a diagnosis of fibromyalgia. No participants withdrew or were removed from the study.	Alpha-Stim CES for 60 minutes daily for three weeks.	Treatment group received active CES treatment. Control group had identical devices, but no current was provided. At the end of the initial three-week period, the groups were unblinded, and participants in the sham group were given the opportunity for three weeks of active CES treatment.	Profile of Mood States (POMS): The active CES group had significantly decreased anxiety scores ($p<0.01$), tender points ($p<0.01$) and pain ($p<0.01$) compared to the sham group. The sham group was then given active treatment for 3 additional weeks in a crossover design which decreased their anxiety scores significantly ($p>0.001$).

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
http://www.Alpha-Stim®.com/wp-content/uploads/FDA-AUGUST-5-2013-515i-Supplement.pdf	Price (2013). United States	Survey	714 civilian, veteran, and service members with an anxiety disorder and 146 veterans and service members with PTSD, responding to a post marketing survey, indicating they were using Alpha-Stim to treat an anxiety disorder, including PTSD.	Survey respondents were using Alpha-Stim as needed to treat anxiety disorders.	N/A	82.9% of respondents reported ≥25% fewer anxiety symptoms and clinical improvement with the majority of these respondents reporting ≥50% improvement in anxiety.

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
Dr. Simon Royal, University of Nottingham	Royal (2020 – planned completion) A GP surgery center in the City of Notthingham	Non-randomized controlled trial	[redacted] patients reporting mild to moderate anxiety and depression symptoms requesting mental health care at the GP surgery center [redacted] patients have returned the device ([redacted] due to "anxiety after using illegal drugs" and [redacted] due to a broken screen. [redacted] patients have not provided post-intervention GAD and PHQ-9 scores.	Daily Alpha-Stim use at home for eight weeks	Alpha-Stim CES group and Usual care group	Study is underway. Preliminary results indicate that, [redacted], there are [redacted] in GAD scores posttreatment.
https://www.alpha-stim.com/wp-content/uploads/CES_Research/voris-investigation.pdf	Voris (1995). Delos Mind/Body Institute, Dallas, Texas, USA	Double-blind RCT	105 patients from the Delos Mind/Body institute reporting anxiety or inordinate levels of stress during intake. 35 participants were removed from the study due to an	One 20-minute CES treatment during regular group therapy session.	Participants were divided into three groups, active CES group, sham CES group, and treatment as usual (control group).	The active CES group had significantly lower anxiety scores on the State Anxiety Inventory (SAI) compared to sham group (p=.0001, d=-

			inability to read and write in either English or Spanish.			1.60) and control groups. The active CES group had significantly lower scores on EMG (p=.0001, d=-1.08) and increased scores on finger temperature (p=.0141. d=.50) than sham and control groups, indicating physiological proof of less anxiety.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

The following studies are presented as key evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Study	Results	Company comments
Morriss et al. (2019)	Of 161 patients recruited, 72 (44.7%) and 77 (47.8%) achieved remission on the GAD-7 at 12 and 24 weeks respectively with 122 (75.8%) receiving at least 6 weeks CES. Mean (SD) GAD-7 score at baseline significantly improved from 15.77 (3.21) to 8.92 (5.42) and 8.99 (6.18) at 12 and 24 weeks respectively ($p<0.001$). 80 (49.7%) participants required further individual CBT. CES provided a saving of £540.88 ($684.68) per patient. The proportions of participants achieving reliable improvement on the GAD-7 were 102 (63.4%) and 105 (65.2%) at 12 and 24 weeks respectively. No patient showed reliable deterioration at 12 or 24 weeks. The vast majority of the drop in GAD-7 is experienced in the first 6 weeks and there is no statistically significant difference between week 6 and any subsequent time point up to week 24.	This open label study has a large sample size and robust results that provide confidence in the findings. The reductions in anxiety, depression, and insomnia demonstrated in this study are consistent with the results of other studies evaluating the effectiveness of Alpha-Stim, which provides confidence in the validity and utility of the results.

Barclay & Barclay (2014)	There were highly significant differences between the active and sham groups for both anxiety and depression from baseline to endpoint of study The HAM-A scores decrease in the active group of 32.8% (19.89 to13.37) was more than 3 times the mean decrease of 9.1% (21.98 to 19.98) on the HAM-A for the sham group. The HAM-D_{17} scores decrease in the active group of 32.9% (9.64 to 6.47) was more than 12 times the mean decrease of 2.6% (10.22 to 9.96) on the HAM-D_{17} for the sham group. 83% of the active CES group had a decrease of ≥ 50% decrease in anxiety scores on the HAM-A from baseline to endpoint of study. 82% of the active CES group had a decrease of ≥ 50% decrease in depression scores on the HAM-D_{17} from the baseline to the endpoint of study.	This is a very strong double-blind RCT study. Participants had to meet criteria for an anxiety disorder to be included in the study. The results indicate very strong reductions in both anxiety and depression symptoms resulting from Alpha-Stim treatment. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Voris (1995)	Spielberger's State Anxiety Inventory was used to measure anxiety. The scale has established reliability and validity. Physiological measures, EMG, EDR and finger temperature, which are indications of decreased anxiety were also measured to validate level of anxiety. The active treatment group demonstrated significantly lower levels of anxiety posttreatment on both physiological and self-report measures than either the sham or control groups.	This was the first Alpha-Stim CES study that used the Alpha-Stim masked, sham controlled, randomized clinical trial research protocol. The study has served as a foundation for the development of RCTs on the effectiveness of CES for the treatment of anxiety. Strengths of the study are (1) the rigor of the research design and the use of 3 groups- active, sham and control, (2) the study was adequately powered with an N of 105, (3) diagnosis of an anxiety disorder was confirmed by a psychiatrist, (4) the research team, participants and statistician were masked to the identity of the devices, and (5) the use of a valid subjective state anxiety scale (SAI) confirmed by objective physiological measures of anxiety. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Lu & Hu (2014)	**Hamilton Anxiety Scale (HAM-A).** The treatment group which consisted of daily Paxil and CES improved significantly more than the control group which received Paxil alone. Both the control and the treatment group showed improvement in HAM-A scores with each consecutive measurement indicating Paxil is effective in relieving anxiety. The comparison of HAM-A scores showed no significant changes between control and treatment groups at baseline, week 2 or week 4 however there was a significant difference in the 2 groups at week 6 ($p<0.01$).	This study indicates that CES treatment can be used in conjunction with Paxil to improve the effectiveness of anxiety treatment. The authors state that, in the treatment group, "18 cases were cured," a claim not often seen in mental health research. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Lee et al. (2013)	Anxiety scores were reduced significantly in the CES group compared with the control group ($P<0.016$) and withdrawal scores during rocuronium injection were also reduced significantly in the CES group compared with the control group ($P<0.049$). The pain score was significantly lower at 1 and 4 hours post-surgery in the CES group compared with the control group. The number of patients who needed additional analgesia was not significantly different – and ACTH, cortisol and glucose levels were also not significantly different – between the two study groups.	This double-blind RCT study demonstrates the effectiveness of Alpha-Stim CES treatment in lowering situational anxiety in a stressful situation such as pending surgery for cancer treatment. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Koleoso et al. (2013)	Significant reduction in anxiety was seen between all three treatment groups and the control group. The anxiety reduction was not significantly different between the three treatment groups, indicating relaxation alone, CES alone, and combined relaxation and CES are equally effective in reducing anxiety. The study concludes that each of these treatments are effective alternatives to anxiolytic medications.	Strength of this clinical study include: (1) The use of a randomized quasi-experimental research design that had pre-post measures; (2) use of valid and reliable MDAS scale; and (3) The cut-off score for dental anxiety on the MDAS in this study was established in a previous pilot study. The finding of this study is that CES significantly decreases dental anxiety, is as effective in decreasing anxiety as relaxation, and is easier to use than learning relaxation techniques is consistent with previous findings by Gibson et al. (1987) and other studies. This consistency provides confidence in the validity and utility of the results of this study.

Kim et al. (2008)	There was no difference in anxiety score of waiting room measurements between the control and CES groups. However, control group showed significant elevation in operating room score compared to waiting room measurement. CES group showed significant reduction of anxiety score in the operating room compared to waiting room measurement. Hemodynamic changes of blood pressure and pulse rate in the operating room were significantly elevated in both control and CES groups. Value for CES group operating room score was significantly lower than that of control group.	Strengths of this study include: (1) The randomized controlled clinical trial design (2) An adequate N of 60 to detect differences between the active and sham groups and (3) The blinding of the investigators to which subjects received CES treatments. The use of a sham CES device would have increased the strength this study. The findings of lower anxiety in the treatment group in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Lichtbroun et al. (2001)	At the end of the 3-week RCT phase, The active CES group had significant findings on 8 of the 11 variables compared to the sham group: significantly lower anxiety scores (p=0.04, d=-.60), higher quality of sleep scores (p=0.02, d=.45), lower pain scores (p=.004, d=.65), higher feelings of well-being scores (p=.007, d=.73), higher quality of life scores (p=.000, d=.97), lower fatigue scores (p=0.03, d=-.72 and lower anger scores (p=0.04, d=.60) compared to sham group. The treatment effect sizes between active CES and sham group ranged from -.36 to .97 on 8 significant variables, with a pooled effect size of .64. After completion of the RCT arm, 23 of the 40 sham or control patients opted for actual CES in an open label crossover arm where they could increase the current in accordance with the standard clinical protocols for Alpha-Stim CES. When compared to baseline results, there were significant reductions in self-reported pain, tender-point pain ratings, and fatigue as well as highly significant improvements in sleep quality, feeling of well-being, and vigor.	Strengths of this study are: use of a randomized, sham controlled, double-blind design (the investigators chose to use the Alpha-Stim RCT research protocol for the study); active and sham Alpha-Stim devices were pre-set and locked at the designated levels for each specific group for current level and time by the manufacturer at the factory and sham units were the same as active units, except they did not emit electricity; randomization of devices was done by the manufacturer and followed according to the protocol by the investigators; use of 3 groups, active, sham and the control group; and the structured and detailed protocol for the CES treatments for both active and sham groups. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Winick (1999)	The mean value for the dentist's and patients' baseline evaluations tended to be higher in the treatment group at the start probably due to the more severe procedures in that group compared to the sham group but was not significant. The active CES group had lower anxiety scores (VAS) from baseline to endpoint of the study than the sham group as measured by the investigator ($p<.02$) and subjects ($p<.02$), see figure below**.** Findings using an inverse Likert scale corroborated these findings for both the investigator evaluation ($p<.01$) and subjects' evaluation ($p<.01$).	Strengths of this study include: (1) use of a randomized, sham controlled, double-blind design; (2) active and sham Alpha-Stim devices were pre-set at the designated levels for each specific group for current and time; (3) sham devices were the same as active devices except they did not emit electricity; (4) all participants had common dental procedures such as fillings, crowns or bridge, or dental exams and cleaning; (5) all participants reported dental anxiety at baseline in order to be in the study; (6) an inverse Likert scale was used post-test as a method to corroborate the findings from the VAS scale; and (7) the participants, investigator and staff were all masked as to the condition of the device. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Gibson & O'Hair (1987)	Participants responded on the STAI significantly ($P<.001$) better than controls and equally to either RT alone with a means of 52.88 pretest to 32.19 post, CES alone: 52.31 pre to 30.06 post, or both RT and CES together: 53.69 pre to 30.44 post. The control group only dropped from 53.25 to 51.94. The EMG trend paralleled the STAI with means of 15.64 µV to 11.10 post-test in the RT alone, 17.12 to 11.17 µV in the CES alone, 17.41 to 9.77 µV in the combined group, and 14.14 to 14.47 µV in the control group. Analysis of variance for EMG scores showed highly significant F-ratios for the time variance term and the group X time interaction term. Results were further verified by Tuckey's tests for pair-wise comparisons.	This early study demonstrates the effectiveness of Alpha-Stim CES treatment in improving anxiety symptoms utilizing both self-report and physiological measures. While there was no significant differences between CES and relaxation training groups, CES treatment is easier to administer and requires less effort from the patient, therefore is more likely to be complied with. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Cork et al. (2004).	The Pain Intensity Score, the Tenderpoint Score, and the POMS Score were all significantly less in the CES Group compared to the Sham Group at 3 weeks ($p<0.01$). For those patients in the Sham Group who elected to receive treatment with CES over the subsequent 3-week period, all measurements except the Oswestry Score were significantly improved over baseline ($p<0.001$).	Strength of this study are: use of a double-blind, sham controlled RCT design; the active and sham devices were preset for time and current level, and the sham CES device was identical to the active CES device except they did not emit electricity; the study was adequately powered with an N of 74, based on the research on the effect sizes for CES for treatment of anxiety. This 2004 study measured general anxiety using the POMS scale which was commonly used at that time and has established clinical and research utility in the literature. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Kirsch et al. (2019)	Data were analyzed using the student t-test (unpaired) comparing pre and posttest measurements. The statistical analyses revealed highly significant improvement ($p<0.001$) in anxiety, depression, insomnia, and pain. The effect size Cohen's d values from a total of 237 treatments were greater than 2 standard deviations for all outcome measures indicating a high level of practical change from baseline to posttest supporting the capability of Alpha-Stim CES technology in reducing self-perceived symptoms and the ability to monitor progress on the Alpha-Stim app.	This study demonstrates the effectiveness of Alpha-Stim treatment when used in real world settings with members of a stressful and demanding profession. The findings of this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Morrow et al. (2019)	Treatment with AS-M and LTO were both associated with statistically significant reductions in pain severity (BPI), pain interference (BPI), daily pain intensity scores (daily pain log), and pain catastrophizing (PCS). Use of AS-M was associated with statistically significant improvements in depression (BDI), anxiety (BAI), and distress (SUD) scores. In addition, veterans completing AS-M treatment showed a statistically significant improvement in self-reported relaxation scores. Nonpharmacologic, noninvasive devices pose fewer risks and seem to be more effective in reducing pain intensity than traditional treatments, including medications or surgical intervention. In light of the current emphasis on evidence-based health care and as the evidence for the effectiveness of noninvasive pain devices modalities grows, it is likely that treatments incorporating modalities such as microcurrent electrical therapy (MET), CES, and LTO will become common options for managing chronic pain.	This study has a large sample size and highly significant results, adequately demonstrating Alpha-Stim treatment is effective in managing anxiety, even in patients with chronic and persistent pain. The results of this study are consistent with previous studies and surveys, which provides confidence in the validity and utility of the results.
Yennurajalingam et al. (2018)	33/36 (92%) completed the CES course of treatment. Median (IQR) adherence CES use and satisfaction scores were 93% (89-100) and 10 (9-10) respectively and the adherence criteria was met in the study. CES use was safe (no grade 3 or higher adverse events). HADS anxiety ($p<0.001$), HADS depression ($p=0.024$), ESAS anxiety ($p= 0.001$), depression ($p=0.025$), BPI pain ($p=0.013$), PSQI daytime dysfunction ($p=0.002$), and Medication use ($p=0.006$) scores improved after 4 weeks of CES treatment.	This study demonstrates the effectiveness and safety of treatment with Alpha-Stim in a population with a terminal and painful illness. Participants experienced highly significant reductions in anxiety and depression. Medication use also significantly improved within the 4-week trial. The findings of this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Gong et al. (2016)	After treatment, the participants in the experiment group had significantly lower scores of the Self-rating Anxiety Scale (SAS), the Self-rating Depression Scale (SDS), and Wexner constipation score than the control group (all $p< 0.05$). The number of successful expulsions in the experiment group was larger than the control group ($p= 0.016$).	This study demonstrates the ability of Alpha-Stim CES to reduce not only anxiety and depression symptoms, but also to positively affect physical symptoms related to psychological distress. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Libretto et al. (2015)	All health-related outcomes (PTSD, depression, anxiety, pain, and resilience) show statistically significant improvements from pre- to posttreatment. Patient satisfaction with Alpha-Stim CES increased steadily throughout the four years it was utilized in Reset, from 74.1% to 100% patient satisfaction.	This large retrospective study demonstrates that Alpha-Stim CES can be used in conjunction with traditional and other treatment approaches. The findings of anxiety reduction in this population of veterans with PTSD and other mental health disorders, are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Kirsch et al. (2014)	**7 point Likert scale: Anxiety (N=114).** Of the total group, 46.5% reported less anxiety and clinical improvement of ≥ 50% while 20.2% reported clinical improvement of anxiety between 25-49%. In the total group, 66.7% respondents reported ≥ 25% improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of ≥ 50% while 15.4% reported clinical improvement of anxiety between 25-49% for a total of 73.1% of respondents who reported less anxiety and clinical improvement ≥ 25%. In the CES and medications group, 43.2% of respondents reported decreased anxiety and clinical improvement ≥ 50% while 21.6% reported decreased anxiety 25-49% improvement for a total of 64.8% of respondents who reported decreased anxiety and clinical improvement ≥ 25%. **PTSD (N=88**). Of the total group, 38.6% reported less anxiety and clinical improvement of ≥ 50% while 23.9% reported clinical improvement of anxiety between 25-49%. In the total group, 62.5% respondents reported ≥ 25% improvement in anxiety. In the CES only group (no medications), 50.0% reported decreased anxiety and clinical improvement of ≥ 50% while 22.2% reported clinical improvement of anxiety between 25-49% for a total of 72.2% of respondents who reported less anxiety and clinical improvement ≥ 25%. In the CES and medications group, 35.7% of respondents reported decreased anxiety and clinical improvement ≥ 50% while 24.3% reported decreased anxiety 25-49% improvement for a total of 60.0% of respondents who reported decreased anxiety and clinical improvement ≥ 25%.	This survey explores the use of Alpha-Stim CES with veterans and service members issued the device from either a VA or Department of Defense (DoD) medical facility. Thus, the participants have been diagnosed with an anxiety disorder or with PTSD and are using Alpha-Stim, either alone or in conjunction with psychotropic medication, in real-world conditions to treat their symptoms. This results of this survey show highly significant reductions in anxiety and PTSD symptoms, and that the patients who use the device without concomitant psychotropic medications are highly satisfied with the effectiveness and safety of the device. When compared to results from a WebMD online survey, Alpha-Stim is consistently rated with higher satisfaction and effectiveness results than the more commonly prescribed medications for anxiety and PTSD. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Price (2013)	99.9% of respondents stated Alpha-Stim CES was safe and effective in treating their symptoms. 36% of respondents treating anxiety disorders stated Alpha-Stim was the most effective treatment method they had tried. 82.9% of respondents indicated improvement in their anxiety symptoms, and 89.7% of respondents with PTSD indicated improvement in their symptoms.	This post market survey indicates the experiences of patients using Alpha-Stim CES for treatment in real world conditions. The respondents to this survey overwhelmingly indicate that Alpha-Stim is safe and effective in treating their conditions. The majority of patients utilizing Alpha-Stim to treat anxiety or PTSD report improvement in their symptoms. The findings of anxiety reduction in this survey are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Overcash (1999)	A numerical rating scale (NRS), 0-100, with 100 being the "highest amount of anxiety they can imagine" and 0 being no anxiety. The following physiological indices of anxiety were also measured; electromylegram (EMG), Electrodermal response (EDR), and peripheral temperature. All of these measures, whether subjective or physiological, demonstrate significant reductions in anxiety from pre- to post-treatment.	Strengths of this study are: it was adequately powered with a large N of 197 subjects, both subjective and objective physiological measures of anxiety were used, and an analysis of the data was done comparing outcomes by the therapist's level and type of training in order to determine if the effect was from CES or from the therapist (there were no significant differences in outcomes by level of training of therapist). The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.
Royal (2020) – in progress	[redacted] (as measured by the GAD) from pretreatment to posttreatment are [redacted] In addition, the information provided by Dr. Royal includes feedback from the patients regarding their experience with Alpha-Stim. These comments include: "[redacted]	The timing of this study occurred so that participants, and the resulting data, are influenced by an international pandemic, COVID-19. As a result of this pandemic, many countries have implemented social distancing or quarantine measures to limit the spread of the virus. The anxiety regarding this pandemic and the effect of drastic, rapid changes in the lives of the participant, are likely increasing their baseline anxiety and depression. However, [redacted] this study [redacted]. These preliminary findings of [redacted]

The following studies are presented as supporting evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Study	Results	Company comments
Platoni et al. (2019)	Analysis of the results was done by measuring the differences between the pretest and posttest mean of the participants. For anxiety, the pretest mean was 4.18 and the posttest was 1.93 producing a reduction in anxiety of 54% with p<.001, and Cohen effect size d=1.21 (large). Similar results were seen in insomnia with a pretest mean of 5.70 and posttest mean of 3.80 for a reduction of 33% with p<.001 (two-tailed), and effect size d=1.18 (large), depression measures were a pretest mean of 3.95 and posttest mean of 2.83 for a reduction of 28% with p<.001 (two-tailed), and effect size d=.81 (large) and the pain pretest mean was 4.62 and posttest mean of 2.58 for a reduction of 44% with p<.001, and effect size d=.72 (large).	This study has a large sample size and further demonstrates the effectiveness of Alpha-Stim treatment when used in real world settings with members of a stressful, traumatic, and demanding profession. The findings of this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Lande & Gragnani (2018)	There was significant increase (p=.000) in the higher beta frequencies following the 20-minute CES treatment. The increase in beta frequencies persisted 10 minutes (p=0.000) after the CES treatment was concluded while slower wave activity significantly decreased (p=0.014 and p=0.049). There was also a significant difference (p=.000) in the subjective units of distress before CES (mean=4.12) and after CES (mean=3.26). Brain wave measurements taken immediately after the 20-minute CES session showed a significant and strong effect in the beta region, suggesting an increase in mental alertness, focus and concentration. Significant changes were seen as quickly as 10 minutes and the strong effect in the beta region persisted through the 10-minute follow up, indicating increased mental alertness. Participants also reported significant reduction in distress following the CES treatment. This finding may be related to the increase in beta wave activity. Improved mental focus and corresponding decrease in distraction may be a welcome relief among individuals with overlapping anxiety, depression and trauma symptoms as reflected in this study group.	This study found highly significant reductions in reported distress before and after CES treatment. Furthermore, this study found highly significant increases in beta waves during and in the minutes immediately following treatment, which corresponds with increased feelings of alertness. These changes in brain waves demonstrate a physiological affect from CES treatment, which corresponds with feelings of reduced anxiety and emotional distress. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

Mellen & Mackey (2009)	Reductions in anxiety, as measured by the BAI and the BSI, were nonsignificant between the control and treatment group, the reductions in depressive symptoms, as measured by the BDI and BSI, were significant. Furthermore, a trend analysis indicates a positive change in overall psychological functioning, indicating that Alpha-Stim CES provides a global brain modulation, rather than the targeted approaches of psychotropic medications. The trend toward reductions in the psychiatric symptoms measured by the BSI (to include anxiety, psychoticism, anger/hostility, and depression) translate into less distressed officers and improved performance at work and home.	There was no significant difference on anxiety scores between the active CES and sham group on either the Beck Anxiety Inventory (BAI) or Brief Symptom Inventory (BSI) anxiety measures. The unexpected non-significant result for anxiety was inconsistent with the investigators' prior study on this population (see Mellon & Mackey 2008) and is most likely due to a protocol deviation. Because of a heavy workload for subjects who were parole officers, outcome measurement of state (situational) anxiety and depression were rescheduled and done one week after the final CES treatment. While the findings for depression were stable and remained significant (The active CES group had significantly lower depression scores on the BDI ($p<0.05$) and the BSI-D ($p< 0.01$) than the sham group), post-test evaluations for state anxiety should have been done immediately after the completion of the last CES treatment as state anxiety varies depending on the immediate situation. This is the most likely reason for the non-significant anxiety findings taken one week after the final CES treatment.

Mellen & Mackey (2008)	No changes were found between pre- and post-assessment means for the control group. However significant changes were found in the treatment group's BSI results, suggesting a positive influence from using CES. In addition, the treatment group findings support the argument that Alpha-Stim CES provides a global brain modulation. Differences in pre/post-treatment means for the treatment group were: 1. Somatization: measures bodily complaints (P<.008), 2. Obsessive/Compulsive: repetitive thoughts and actions (P<.020), 3. Interpersonal Sensitivity: difficulties with interpersonal relationships (P<.077), 4. Depression: sad mood, loss of energy, difficulty sleeping or sleeping too much (P<.015), 5. Anxiety: excessive worry, (P<.015), 6. Hostility: feelings of anger toward others and the world (P<.077), 7. Phobia: excessive fearful reactions toward objects, insects and such (P<.177), 8. Paranoia: excessive fears that are not supported by evidence (P<.066), 9. Psychoticism: these individuals can appear unusual and emotionally distant (P<.050). The BPI also has 3 global scales for measuring stress: 1. Global Index: the most sensitive measure of stress (P<.007), 2. Positive Symptom Distress: degree of stress being reported (P<.042), and 3. Positive Symptom Total: total number of symptoms endorsed by a subject (P<.004).	Post treatment comments by the officers using Alpha-Stim were generally favorable, including statements of feeling calmer, having thoughts that are less negative, and being relaxed and "ready to face the day." These comments support the trend toward positive changes in psychological distress as demonstrated in this study. The findings of anxiety reduction in this study are consistent with prior studies and surveys, which provides confidence in the validity and utility of the results.

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

The following studies are presented as key evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Morriss et al. (2019) Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder	
How are the findings relevant to the decision problem?	Alpha-Stim was utilized in this study to examine the safety and effectiveness of treating Generalized Anxiety Disorder.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** This study shows that in moderate to severe treatment seeking patients with GAD in the UK, nearly 45% of patients achieved remission and 63% achieved reliable improvement in their self-rated anxiety symptoms with Alpha-Stim CES treatment. These improvements were maintained for a further 12 weeks after CES was completed whether or not patients received iCBT. 2) **Increased treatment choices for people with anxiety disorders:** This study demonstrated that Alpha-Stim CES treatment is an effective choice for treatment of anxiety. 3) **An alternative management to pharmacological and/or psychological treatments:** Patients in this study had failed trials with anti-anxiety medications and were on a waiting list for iCBT. The study demonstrated that Alpha-Stim was effective in helping patients achieve recovery or remission in their anxiety when pharmacological approaches had been unsuccessful. 4) **Home use for potential reduction in time and cost associated with attending appointments:** Patients in this study utilized the device daily from home with minimal follow ups with investigators in a medical clinic.

Morriss et al. (2019) Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder	
Will any information from this study be used in the economic model?	Yes. Compared to a standard course of iCBT (eight sessions or longer), Alpha-Stim CES reduced costs of care by £540 or more per patient. Therefore, Alpha-Stim CES is a cost-effective treatment alternative for patients with anxiety disorders.
What are the limitations of this evidence?	There was no control group and the study was not a randomised control trial.
How was the study funded?	The study was supported by Electromedical Products International, Inc., by loaning devices for the study. The chief investigator's time was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East Midlands and Nottingham NIHR Biomedical Research Centre. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Royal S (2020) To evaluate the effectiveness and acceptability of a new patient pathway used in the management of mild to moderate anxiety and/or depression in adults presenting to primary care.	
How are the findings relevant to the decision problem?	Alpha-Stim was utilized in this study to examine the safety and effectiveness of treating anxiety and depression among patients requesting mental health treatment at a surgical GP center.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** This study shows that [redacted], Alpha-Stim is [redacted] the anxiety for the [redacted] of participants using this device. 2) **Increased treatment choices for people with anxiety disorders:** This ongoing study demonstrates that Alpha-Stim CES treatment is [redacted] choice for treatment of anxiety. 3) **An alternative management to pharmacological and/or psychological treatments:** Patients in this study are utilizing Alpha-Stim treatment in lieu of routine care. 4) **Home use for potential reduction in time and cost associated with attending appointments:** Patients in this study utilized the device daily from home with minimal follow ups with investigators in a medical clinic.
Will any information from this study be used in the economic model?	No – study is not complete and data regarding cost effectiveness has not yet been provided
What are the limitations of this evidence?	This is an ongoing study, and the data presented are not yet comparing the Alpha-Stim group with the routine care group.
How was the study funded?	The is being funded by NIHR CRN East Midlands, with is providing financial support to The University of Nottingham Health Service for the study. The funders of the study have no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. Electromedical Products International, Inc. has supported the study by providing Alpha-Stim devices for use.

Kirsch TB, et al. (2019) A novel medical device that relieves anxiety, depression and pain while improving sleep in a population of teachers	
How are the findings relevant to the decision problem?	This study demonstrated significant reductions in anxiety with real-world use of Alpha-Stim.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** This study shows highly significant decreases in self-rated anxiety scores among teachers using the Alpha-Stim device. 2) **Home use for potential reduction in time and cost associated with attending appointments:** Participants in this study were trained on the device and were able to easily use them at home and record their distress levels before and after treatment utilizing a smart phone app.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	A limitation of this study is self-selection by teachers into the study. A second limitation is the lack of a control or comparison group against which results could be statistically and practically compared.
How was the study funded?	The Brazos Foundation, an independent charity in Mineral Wells, TX, paid for participants to be seen by two local nurse practitioners for a health screening and to write orders for Alpha-Stims. Electromedical Products International, Inc, donated the devices and participants were able to keep the $795 devices for participating in the study.

Morrow et al. (2019) Nonopioid alternatives to addressing pain intensity: A retrospective look at two noninvasive pain treatment devices	
How are the findings relevant to the decision problem?	This study demonstrated significant decreases in anxiety among veterans with chronic or persistent pain with Alpha-Stim treatment.
Does this evidence support any of the claimed benefits for the technology? If so, which?	1) **Improvement in anxiety and depression symptoms:** Use of AS-M was associated with statistically significant improvements in anxiety on the Beck Anxiety Inventory (BAI). Depression (as measured by the BDI) was significantly reduced from a preintervention mean of 24.62 to a postintervention mean of 14.38 ($p<0.01$). In addition, veterans completing AS-M treatment showed a statistically significant improvement in self-reported relaxation scores. 2) **An alternative management to pharmacological and/or psychological treatments:** Devices such Alpha-Stim are well suited to interdisciplinary treatment because they are not seen as being under the purview of a specific health care specialty.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	The limitations of the study are the use of retrospective, quality improvement evaluations of outcomes from a single clinic. Because analyses were conducted as part of a quality improvement effort, veterans were offered a specific device based on clinical indications, there were no comparisons between devices, and there was no comparison group.
How was the study funded?	This study was conducted by the Eastern Oklahoma VA Health Care System. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim M devices for use.

Yennurajalingam et al. (2018) Cranial electrotherapy stimulation for the management of depression, anxiety, sleep disturbance, and pain in patients with advanced cancer: A preliminary study	
How are the findings relevant to the decision problem?	The participants with advanced cancer diagnoses also had to demonstrate moderate to severe anxiety or depression symptoms to be included in this study.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** Participants demonstrated significant reductions in both anxiety and depression during the four-week trial. 2) **Increased treatment choices for people with anxiety disorders:** Treatment with Alpha-Stim resulted in immediate and long-lasting reductions in anxiety and depression despite participants being in palliative care for cancer. These results demonstrate that Alpha-Stim can be utilized as a treatment option for anxiety and depression in this population. 3) **An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** This study found that use of CES was feasible for treatment of symptoms in advanced cancer patients and was associated with significant improvements in, among other symptoms common with this population, anxiety and depression. Use of sedative medication was also significantly reduced during the 4-week trial.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The main limitation in this evidence is lack of a sham control group. Also, extra doses of analgesics participants may have been taking were not measured, and this may be a limitation in interpreting the results.
How was the study funded?	This study was conducted by the University of Texas MD Anderson Cancer Center. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Gong et al. (2016) Efficacy of cranial electrotherapy stimulation combined with biofeedback therapy in patients with functional constipation	
How are the findings relevant to the decision problem?	This study found significantly greater reductions in anxiety with the CES plus biofeedback treatment (BFT) group than with the group undergoing only BFT.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** The reductions in anxiety and depression for the group undergoing both CES and BFT were significantly greater than the reductions for the BFT group alone. Additionally, these reductions in psychological distress correlated with reductions in the physical symptoms of functional constipation. 2) **An alternative management to pharmacological and/or psychological treatments:** This study demonstrates that CES treatment is an effective and safe alternative to more traditional methods of anxiety treatment for people with functional constipation. **3) An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** This study points out that psychotropic medications can become habit forming (requiring increased dosages) and bring out side effects that can adversely impact quality of life for the patient. In contrast, CES is safe, effective, and has no moderate or severe adverse events. 4) **Home use for potential reduction in time and cost associated with attending appointments:** As stated in this study, Alpha-Stim "is of a small size such that it can be carried conveniently and can be used repeatedly to save medical resources."
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Neither participant nor research staff were blinded to group allocation.
How was the study funded?	Under "Financial Support," this study states, "None." Therefore, the study was most likely funded by the Nankai University affiliated hospital. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Libretto et al. (2015) Effects of integrative PTSD treatment in a military health setting	
How are the findings relevant to the decision problem?	The use of Alpha-Stim CES in this integrative multi-modal, multiphase treatment program contributed significantly to reduction in anxiety and PTSD symptoms in the participants.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** Participants in this PTSD treatment program that utilized Alpha-Stim CES, along with other alternative modalities and traditional treatment approaches, experienced highly significant reductions in anxiety and depression symptoms. 2) **Increased treatment choices for people with anxiety disorders:** This study utilized multiple choices for treatment options as part of the program. The effectiveness of Alpha-Stim CES as a treatment option is reflected in the very high patient satisfaction ratings for the device. 3) **An alternative management to pharmacological and/or psychological treatments:** Psychotropic medications typically prescribed for PTSD are minimally effective and have significant side effects. The use of Alpha-Stim CES as an alternative therapy in this study indicates this device is a safe and effective alternative to treatment with medications.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations to the study include lack of a follow-up point to gauge if positive gains were sustained over time, lack of a comparison group, and lack of randomization, which would have limited alternative causal explanations.
How was the study funded?	U.S. Army Medical Research and Materiel Command.

Barclay & Barclay (2014) A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression	
How are the findings relevant to the decision problem?	This study investigated the effects of Alpha-Stim CES treatment on individuals meeting criteria for a diagnosis of an anxiety disorder. The findings indicate Alpha-Stim CES treatment is highly effective in reducing anxiety and depression symptoms in this population.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** The treatment group had improvement in anxiety symptoms 3 times greater than the sham group, and improvement in depressive symptoms more than 12 times greater than the sham group. **2) Increased treatment choices for people with anxiety disorders:** The highly significant reductions in anxiety symptoms found in this study indicate that Alpha-Stim CES is a very effective treatment choice for people with anxiety disorders. 3) **An alternative management to pharmacological and/or psychological treatments:** The improvement of symptoms with Alpha-Stim CES treatment in this study demonstrates that this treatment approach is a highly effective and safe alternative to pharmacological or psychological treatments. **4) An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** There were no side effects reported from Alpha-Stim treatment in this study, and participants were able to utilize the devices in their homes, further indicating that Alpha-Stim treatment is a safe and effective alternative for individuals who cannot travel to appointments or tolerate medications. 5) **Home use for potential reduction in time and cost associated with attending appointments:** The participants utilized the device at home, indicating the ease with which this device can be used outside of a doctor's office, and thus reducing the time and cost associated with attending appointments.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	All participants in the study were diagnosed with GAD, but only 23 of the 115 were diagnosed with MDD, although improvement in depression was shown across the entire active group.

How was the study funded?	This study was conducted in association with Liberty University. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Kirsch et al. (2014) Efficacy of cranial electrotherapy stimulation for anxiety, PTSD, insomnia, and depression: US Military service members' and veterans' self-reports	
How are the findings relevant to the decision problem?	The respondents to this survey received their devices from medical centers, and therefore can be reasonably assumed to have been diagnosed with an anxiety disorder. These survey results show that Alpha-Stim CES is a very effective treatment modality for anxiety disorders and PTSD, with satisfaction and effectiveness ratings higher than those for commonly prescribed psychotropic medications.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** Two-thirds of respondents reported moderate to marked improvement in their anxiety symptoms. 62.5% of respondents reported moderate to marked improvement in their PTSD symptoms. **2) Increased treatment choices for people with anxiety disorders:** Respondents to this study received their devices from military and veterans medical centers as a treatment choice for their anxiety disorders. 3) **An alternative management to pharmacological and/or psychological treatments:** Many respondents were utilizing Alpha-Stim devices to treat their anxiety and PTSD without concomitant psychotropic medications, demonstrating this treatment device as an effective alternative to pharmacological treatment. 4) **An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** Service members and veterans have a high rate of comorbid medical and psychiatric disorders. The results of this survey indicate Alpha-Stim is a very effective treatment alternative for this population. 5) **Home use for potential reduction in time and cost associated with attending appointments:** The respondents in this survey had been trained by their healthcare providers in home use of the device, thus reducing their need to attend a scheduled appointment or walk-in session to use the device, saving both financial and provider resources.
Will any information from this study be used in the economic model?	No.

What are the limitations of this evidence?	A relatively small percentage of respondents invited to participate in the survey responded, most likely due to the fact many of them were active duty service members at the time of purchase and may have discharged from the armed forces or changed their email addresses.
How was the study funded?	Study was part of the post marketing conducted by Electromedical Products International, Inc.

Lu & Hu (2014) A comparative study of anxiety disorders treatment with paroxetine in combination with cranial electrotherapy stimulation therapy	
How are the findings relevant to the decision problem?	The participants in this study were receiving treatment from a hospital for anxiety disorders. This study found that combining CES treatment with Paxil resulted in highly significant improvements in anxiety symptoms.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** The treatment group demonstrated highly significantly more improvement in anxiety symptoms than the control group. **2) Increased treatment choices for people with anxiety disorders:** The results of this study indicate that Alpha-Stim CES significantly improves the results in anxiety treatment when combined with other treatment approaches. 3) **Home use for potential reduction in time and cost associated with attending appointments:** Participants were trained in use of the device in the hospital, then allowed to use the device at home.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	According to the article, the participants from the study come from a single source and observation time is short.
How was the study funded?	This study was conducted at the Mental Health Center of Shenyang City, Shenyang, China Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Lee et al. (2013) Effects of cranial electrotherapy stimulation on preoperative anxiety, pain, and endocrine response	
How are the findings relevant to the decision problem?	While the participants in this study were not diagnosed with an anxiety disorder, per se, they were experiencing high levels of anxiety and psychological distress related to impending surgery for thyroid cancer treatment. The results of this study indicate those treated with CES were significantly less anxious than those who were not treated.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** The participants in the treatment group demonstrated significantly better improvement in anxiety symptoms than the participants in the control group. 2) **An alternative management to pharmacological and/or psychological treatments:** This study indicates that Alpha-Stim CES can be utilized for safe and effective treatment of situational anxiety, providing a possible alternative to sedative or hypnotic medications.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	The study was limited by researchers' failure to consider any possible placebo effects experienced by the control group due to sham treatment. Further research in this area should include three experimental groups: a CES treatment group, a sham group and a placebo-controlled group.
How was the study funded?	This study was funded by a Korea University grant. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Koleoso et al. (2013) The role of relaxation therapy and cranial electrotherapy stimulation in the management of dental anxiety in Nigeria	
How are the findings relevant to the decision problem?	High anxiety scores on the DAS were a prerequisite for inclusion in this study, indicating that anxiety in these participants was at or approaching clinical distress levels. Both CES and CES + relaxation group experienced significant improvement in anxiety in just 3 days of treatment.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** CES treatment contributed to significant reductions in anxiety symptoms for the treatment groups when compared to the control group. 2) **An alternative management to pharmacological and/or psychological treatments:** The study states the results of these treatment approaches provide an effective alternative to anxiolytic medications in treating dental anxiety.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations in this study include small sample size (n=10) for each of the 4 groups and CES treatments were individualized for each subject, thus there was a lack of standardization of CES current.
How was the study funded?	This study was conducted at the Department of Mental Health, University of Ibadan. Ibadan, Nigeria.

Price (2013) Alpha-Stim® user effectiveness survey abstracts in the 2013 supplement information to the CDRH for Alpha-Stim® CES, August 5th 2013.	
How are the findings relevant to the decision problem?	The respondents to this survey are utilizing Alpha-Stim to treat disorders they have been diagnosed with, including but not limited to, anxiety and PTSD. The results of this survey demonstrate real world results in reducing anxiety and PTSD symptoms.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** The vast majority of respondents to this survey report improvement, often marked improvement, in their anxiety and depression symptoms. 2) **Increased treatment choices for people with anxiety disorders:** Respondents to this survey who have been diagnosed with an anxiety disorder or PTSD overwhelmingly reported Alpha-Stim CES is a safe and effective treatment option. 3) **An alternative management to pharmacological and/or psychological treatments:** In addition to reporting Alpha-Stim as a safe and effective treatment, over one-third of respondents stated Alpha-Stim is the most effective treatment method they have utilized. 4) **Home use for potential reduction in time and cost associated with attending appointments:** The respondents to this survey are patients who are using Alpha-Stim CES devices at home to treat anxiety and other psychiatric disorders.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	As this was a post marketing survey, there was no means to control for extraneous variables that may have influenced responses. However, the N for this survey is quite large (2,348), providing validation and confidence in the effectiveness of Alpha-Stim CES in treating anxiety disorders.
How was the study funded?	This survey was conducted at part of the post marketing requirements by Electromedical Products International, Inc.

Kim et al. (2008) The effect of cranial electrotherapy stimulation on preoperative anxiety and hemodynamic responses	
How are the findings relevant to the decision problem?	This study found significant reductions in anxiety for patients in a highly stressful and anxiety-provoking situation. The findings that the control group experienced elevated anxiety, while the CES group demonstrated reduced anxiety, indicates the effectiveness of Alpha-Stim CES in treating all types of anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** The treatment group experienced highly significant reductions in subjectively reported levels of anxiety and physiological indications of anxiety when compared to the control group. 2) **Increased treatment choices for people with anxiety disorders:** The anxiety reduction demonstrated by the treatment group in this study indicates that Alpha-Stim CES is a very effective choice for treating anxiety. 3) **An alternative management to pharmacological and/or psychological treatments:** By utilizing Alpha-Stim CES to treat anxiety in this study, patients did not need other sedentary or hypnotic medications to reduce preoperative anxiety.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	One limitation of this study is failure to use a sham device. The authors identify a limitation being absence of correlation between objective measurement of stress hormone levels (cortisol and catecholamines) and also the fact that surgeries were not confined to the same kind of procedures.
How was the study funded?	This study was conducted by the Department of Anesthesiology and Pain Medicine, Korea University College of Medicine, Seoul, Korea.

Cork et al. (2004) The effect of cranial electrotherapy stimulation (CES) on pain associated with fibromyalgia	
How are the findings relevant to the decision problem?	Patients with chronic pain conditions, such as fibromyalgia, very commonly experience clinical levels of anxiety as a comorbid condition. This study indicates that patients with fibromyalgia experienced significant reductions in anxiety symptoms with Alpha-Stim CES.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** During the RCT portion of the study, the treatment group experienced significant improvement in anxiety symptoms compared to the sham group. When the sham group received three weeks of active CES treatment, they experienced a significant improvement in their anxiety from baseline and midpoint measurements. 2) **Increased treatment choices for people with anxiety disorders:** This study indicates Alpha-Stim CES is a safe and effective treatment option for people experiencing clinical levels of distress from anxiety. 3) **An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** The authors conclude that CES is a safe, effective, and non-invasive treatment option for patients with fibromyalgia. 4) **Home use for potential reduction in time and cost associated with attending appointments:** Participants were able to easily use the devices at home and did not need to visit the clinic to receive treatment.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	This study addresses limitations mentioned in previous studies. Sample size is sufficient, the open label phase allows comparison of the sham group participants, controlling for placebo effect.
How was the study funded?	This study was funded by a grant from the Department of Anesthesiology, LSU Health Sciences Center, Louisiana State University, Shreveport, Louisiana, USA. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Lichtbroun et al. (2001) The treatment of fibromyalgia with cranial electrotherapy stimulation	
How are the findings relevant to the decision problem?	Patients with chronic pain conditions, such as fibromyalgia, very commonly experience clinical levels of anxiety as a comorbid condition. This study indicates that patients with fibromyalgia experienced significant reductions in anxiety symptoms with Alpha-Stim CES.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** During the RCT portion of the study, the treatment group experienced significant improvement in anxiety symptoms compared to the sham group. When the sham and placebo control groups received three weeks of active CES treatment, they experienced a significant improvement in their overall sense of wellbeing, including anxiety symptoms, from baseline and midpoint measurements. 2) **Increased treatment choices for people with anxiety disorders:** This study indicates Alpha-Stim CES is a safe and effective treatment option for people experiencing clinical levels of distress from anxiety. 3) **An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** Although not measured by the study protocol, the authors state most participants in the treatment group reported discontinuing their pain and sleep medications during the 3-week treatment. These reports indicate Alpha-Stim CES was a safe and effective stand-alone treatment. 4) **Home use for potential reduction in time and cost associated with attending appointments:** Participants were able to easily use the devices at home and did not need to visit the clinic to receive treatment.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	A limitation of the data analysis is that it used analysis of variance (ANOVA) and no within or between group effect sizes were included.
How was the study funded?	This study was conducted through the Robert Wood Johnson Medical School, East Brunswick, New Jersey, USA. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Winick (1999) A safe and effective low cost means of anxiety control in a dental practice	
How are the findings relevant to the decision problem?	Participants in this study reported severe levels of anxiety in anticipation of their impending dental procedure as part of the inclusion criteria.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** Active treatment group participants demonstrated significant improvement in anxiety, based on self-report and dentist observation. 2) **Increased treatment choices for people with anxiety disorders:** The author concludes Alpha-Stim CES is a safe, effective, and low-cost alternative for treatment of high levels of anxiety. 3) **An alternative management to pharmacological and/or psychological treatments:** The results of this study indicate that Alpha-Stim CES is a safe and effective means of treating situational anxiety in dental patients, when pharmacological or psychological treatments are impractical. 4) **An alternative option to be used in people with medical comorbidity and disability who might not be able to travel to appointments or tolerate medication:** The author states that many patients requested use of CES at subsequent dental visits and "none objected to it," indicating this option is an effective alternative to hypnotic or sedative medications. 5) **Home use for potential reduction in time and cost associated with attending appointments**: This study utilized Alpha-Stim CES during the dental procedure. The author discusses the low cost to dental practices with this treatment approach.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	The small N (33) in this study could be considered a limitation of the study. However, based on the moderate to large effects sizes for anxiety in the literature, the sample size for this study was large enough to detect a significant difference between the active CES and sham CES groups in favor of the active CES group.
How was the study funded?	This study was conducted through the TMD and Facial Pain Clinic at the New York Eye and Ear Infirmary, New York City, New York, USA. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Overcash (1999) Cranial electrotherapy stimulation in patients suffering from acute anxiety disorders	
How are the findings relevant to the decision problem?	The participants in this study were diagnosed with an acute anxiety disorder as part of the inclusion criteria.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** Results of both subjective and physiological measures demonstrated significant improvement in anxiety symptoms. 2) **Increased treatment choices for people with anxiety disorders:** The results of this study indicate Alpha-Stim CES is a safe and effective choice for treating anxiety disorders. 3) **An alternative management to pharmacological and/or psychological treatments:** More than half of the participants in this study were not taking psychotropic medications during this study. The authors state one motivator for participants was using CES treatment to stay off medications. 4) **Home use for potential reduction in time and cost associated with attending appointments:** Over 80% of participants were loaned a device for home use, thus negating the need to attend an appointment for treatment of their anxiety.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	This was a retrospective study and it has the following limitations; lack of controls; lack of a standard protocol for CES treatments that includes number of treatments, the current level and length of treatment, and for where treatments were done – clinic, home or both places.
How was the study funded?	This study was conducted at Psychological Services, Chambersburg, Pennsylvania, USA. The author purchased the devices used in this study.

Voris (1995) An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among psychiatric patients, impulse control parolees and pedophiles	
How are the findings relevant to the decision problem?	All participants in this study were screened and reported high levels of anxiety or stress as part of the inclusion criteria.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** The treatment group demonstrated significant improvement in anxiety symptoms when compared to the control and sham groups. 2) **Increased treatment choices for people with anxiety disorders:** CES treatment was provided as an adjunct during normal group therapy for anxiety and stress, indicating that addition of Alpha-Stim CES to existing treatment protocols enhances the effectiveness of treatment for anxiety.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	The investigator noted a limitation of the study was the method of randomization based on seating. The general outpatient psychiatric subjects tended to arrive early and select a chair resulting in more of these subjects in the active CES group than in the sham and control groups. There were fewer parolees, who usually arrived later, in the active group and more in the sham and control groups. While the chair method was used to be consistent with the usual routine in group therapy, for future studies the investigator recommended that subjects be assigned by group.
How was the study funded?	This study was conducted through the Delos Mind/Body Institute, Dallas, Texas, USA, and the Dallas Parole Division, Texas Department of Criminal Justice. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Gibson & O'Hair (1987) Cranial application of low-level transcranial electrotherapy vs. relaxation instruction in anxious patients	
How are the findings relevant to the decision problem?	Participants were screened for high levels of anxiety as part of the inclusion criteria for this study.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** The treatment groups, including CES treatment, demonstrated highly significant improvements in anxiety symptoms when compared to the control group, on both self-report and physiological measures of anxiety. 2) **Increased treatment choices for people with anxiety disorders:** This study examined two treatment options for anxiety (relaxation and CES). While there were no significant differences in these two treatment approaches, or the group that combined the two approaches, CES treatment is easier to administer and much more likely to be adhered to. 3) **An alternative management to pharmacological and/or psychological treatments:** The results of this study indicate CES treatment is an effective treatment alternative in reducing anxiety symptoms.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Treatment consisted of a single 20-minute session. While the short-term results are significant, there is no way to measure for long-term effects of treatment or to see if there is a difference in treatment groups with repeated treatments.
How was the study funded?	This study was conducted as part of a doctoral dissertation at the California School of Professional Psychology, San Diego, California, USA.

The following studies are presented as supporting evidence in establishing the effectiveness and safety of Alpha-Stim in treating anxiety.

Platoni et al., (2019) First responder research shows that electrical brain stimulation helps control anxiety, insomnia, and depression	
How are the findings relevant to the decision problem?	This study demonstrated significant reductions in anxiety with real-world use of Alpha-Stim with participants in high-stress professions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** The 86 first responders participating in this study demonstrated highly significant reductions in anxiety and depression. 2) **An alternative management to pharmacological and/or psychological treatments:** Treatment with Alpha-Stim devices was demonstrated to be effective and safe, with no reported side effects. 3) **Home use for potential reduction in time and cost associated with attending appointments:** Participants in this study were trained on the device and were able to use it easily at home and record their distress levels before and after treatment utilizing a smart phone app.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The study was not blinded, and no control group was included. The study used a self-selected group of participants who all used the active device. Time of year may be an unforeseen factor in that stress and symptoms of anxiety and depression may vary based on demands of the job and time of year. The study may have taken place during a period when stress was likely to be decreased/increased, and this factor may have influenced the results.
How was the study funded?	The study was supported by a research grant from the Brazos Foundation, an independent charity in Mineral Wells, Texas, which paid for the health screenings. The devices used in the study were provided free of charge by Electromedical Products International, Inc.

Lande & Gragnani (2018) Prospective study of brain wave changes associated with cranial electrotherapy stimulation	
How are the findings relevant to the decision problem?	This study found significant differences in anxiety among psychiatric patients with severe trauma-related symptoms and sleep problems, and demonstrated changes in brain wave activity correlated with reductions in anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. **1) Improvement in anxiety and depression symptoms:** There was a significant difference in subjective units of distress before and after CES treatment. Observed brain wave changes in alpha, beta, and delta waves correspond with reports of significant reduction in distress following CES treatment. 2) **An alternative management to pharmacological and/or psychological treatments:** This study demonstrates the neurological changes that occur with CES treatment, corresponding with a reduction in reported emotional distress. These changes in brain waves demonstrate that CES treatment is an effective alternate treatment to pharmacological or psychological interventions.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	This open-label study exposed participants to limited interaction, such as positioning the brain wave-sensing headset, with the investigators. While other factors such as the participants' awareness of the stimulation phase of CES may impose a potential bias on the study's results, it is at least partially mitigated by the number of subjects, the strength of the findings, and the value in determining the role of microamperage dosing.
How was the study funded?	This study was funded by the United States Army and conducted at Walter Reed National Military Medical Center. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Mellen & Mackey (2009) Reducing sheriff's officers' symptoms of depression using cranial electrotherapy stimulation (CES): A control experimental study	
How are the findings relevant to the decision problem?	The results of this study indicate the effects of Alpha-Stim treatment result in a more global modulation of brain distress and resulting psychiatric difficulties, to include stress and anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** There was significant improvement in depression symptoms between the control and treatment groups. While improvements in anxiety symptoms were not statistically significant, there was a trend toward improvement in anxiety and other psychiatric symptoms measured by the BSI. 2) **Increased treatment choices for people with anxiety disorders:** The results of this study suggest Alpha-Stim CES has a global modulating effect on brain dysfunctions, providing effective treatment for a wide range of mental health difficulties, including anxiety. 3) **Home use for potential reduction in time and cost associated with attending appointments:** Participants in this study performed normal job duties (other than driving or operating heavy machinery) while wearing the earclips and undergoing CES treatment. This demonstrates how Alpha-Stim CES can be used outside of a provider's clinic.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations of this study include small sample sizes and a deviation from protocol, in that post-treatment evaluations sometimes did not occur for a week after treatment ended.
How was the study funded?	This study was conducted by the Department of Criminal Justice, Jacksonville State University, in Jacksonville Alabama, USA. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

Mellen & Mackey (2008) Cranial electrotherapy stimulation (CES) and the reduction of stress symptoms in a sheriff's jail security and patrol officer population: A pilot study	
How are the findings relevant to the decision problem?	The results of this study indicate the effects of Alpha-Stim treatment result in a more global modulation of brain distress and resulting psychiatric difficulties, to include stress and anxiety.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Yes. 1) **Improvement in anxiety and depression symptoms:** There was a trend toward improvement in anxiety and other psychiatric symptoms measured by the BSI. Post treatment comments made by participants generally reflect considerable reduction in feelings of stress and anxiety. 2) **Increased treatment choices for people with anxiety disorders:** The results of this study suggest Alpha-Stim CES has a global modulating effect on brain dysfunctions, providing effective treatment for a wide range of mental health difficulties, including anxiety. 3) **Home use for potential reduction in time and cost associated with attending appointments:** Participants in this study performed normal job duties (other than driving or operating heavy machinery) while wearing the earclips and undergoing CES treatment. This demonstrates how Alpha-Stim CES can be used outside of a provider's clinic.
Will any information from this study be used in the economic model?	No.
What are the limitations of this evidence?	Limitations of this study include small sample sizes.
How was the study funded?	This study was conducted by the Department of Criminal Justice, Jacksonville State University, in Jacksonville Alabama, USA. Electromedical Products International, Inc. supported the study by loaning Alpha-Stim devices for use.

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

A search of the national regulatory database maintained by the MHRA on March 27, 2020, for the manufacturer (Electromedical Products International, Inc.) as well as for product name (Alpha-Stim) yielded zero results.

A search of the FDA MDR database for both “Alpha-Stim” and “Electromedical Products International, Inc.” with a date range of January 1980 to March 27, 2020 yielded zero results.

A search of the FDA database (Maude) for “Alpha-Stim,” with a date range from January 1, 1980 to March 27, 2020, also conducted on March 27, 2020, yielded the following two results:

1) Report received 12/19/2013:

    a. Event Date 06/23/2013

    b. Event Type Injury

    c. Event Description: Pt called to report adverse reaction to alpha-stim electrode. He stated he used this device as treatment for a phobia of flying. He tried it on (b)(6) 2013, and said he followed the directions and tried the device at the minimum current for the minimum amount of time, which is 20 minutes. Since he used the device, he has been experiencing severe tinnitus. He stated it's been 6 months and he still has the tinnitus and he doesn't know what to do. He stated it's ruining his life. He said he's tried acupuncture, and visited an ent doctor to help his condition, but nothing is helping and the doctor didn't find any problems. He said he feels the company lied to him and that tinnitus was not listed as a possible side effect when using the device. He mentioned that he is considering contacting a lawyer because he doesn't know what else to do. He also stated he read info on the internet, that it has been reported to the fda that people have experienced tinnitus using this device. He is very upset this is not listed as a possible side effect.

    https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=3532948&pc=JXK

2) Report received 10/31/2019

    a. Event Date 10/22/2019

    b. Event Type Injury

    c. Event Description: My acupuncturist used alpha-stim on my earlobes for 20 min. During acupuncture treatment, i experienced intestinal spasms and bloating for 12 hours. Also insomnia, required 2 f/u acupuncture visits to alleviate symptoms.

    https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=9266356&pc=GZJ

Company response: Electromedical Products International, Inc. have made several attempts to contact this patient to investigate her complaints. However, to this date, she has not responded to the attempts to communicate with her.

In addition to the two reports to the FDA described above, there were 56 reported adverse events reported to Electromedical Products International, Inc. between 2012 and 2019. Every reported adverse effect was deemed mild and self-limiting. Adverse events from using Alpha-Stim® CES reported to EPI between 2012-2019 were <1%. This is consistent with the below review of 12 Alpha-Stim® CES studies where adverse events reported from using Alpha-Stim® CES were also <1%.

The table below demonstrates the favorable safety profile of Alpha-Stim® CES over the 8-year period between 2012 and 2019.

Year	Adverse Effects Reported	Type of Adverse Effect
2012	6	6 Skin Irritation
2013	3	3 Skin Irritation
2014	1	1 Skin Irritation
2015	4	2 Skin Irritation, 1 Leg Pain, 1 vasovagal response
2016	2	1 Dizziness/Tinnitus, 1 Paradoxical Reaction
2017	4	4 Skin Irritation
2018	11	5 Paradoxical Reaction, 3 Dizziness, 2 Headache, 1 Skin Irritation
2019	25	17 Skin Irritation/Burn, 3 Paradoxical Reaction, 2 Tinnitus, 1 Nausea, 1 Headache, 1 Intestinal Spasms/Bloating and Insomnia
Total	**56**	

Adverse events reported to Electromedical Products International, Inc. 2007-2019.

As indicated in the following table, there were 132,249 Alpha-Stim devices sold between January 1, 2012 and December 31, 2019. When comparing the number of units sold to the number of reported adverse events, the ratio is 0.04%, clearly demonstrating the safety of CES in real world conditions.

Alpha-Stim SCS	20,826
Alpha-Stim 100	4,457
Alpha-Stim AID	55,319
Alpha-Stim M	51,647
TOTAL	132,249

Total devices sold over 8 years between January 2012 and December 2019

One can hardly make a comparison between CES side effects and the side effects of FDA approved psychotropic medications commonly prescribed for anxiety. There are fewer side effects for CES than for any medication, and the side effects are much milder and far more self-limiting than those for most commonly prescribed psychotropic medications.

In fact, no serious adverse events have ever been reported in the 39 years that Alpha-Stim CES has been on the market. Minor side effects reported through the years are all self-limiting and rare (< 1%) consisting mainly of dizziness and headache when the current is set too high in sensitive individuals and local skin irritation at the electrode site.

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

The vast majority of the clinical literature detailed above indicate no adverse events were reported by participants. As the tables below indicate, in the clinical literature on Alpha-Stim CES, no serious adverse effects have ever been reported, and the adverse effects that are reported are very rare (<1%), mild, and self-limiting. Thus, the reports of adverse effects in the clinical literature is consistent, both in rate and severity, of events reported to Electromedical Products International, Inc. regarding use of Alpha-Stim devices in real-world setting to treat diagnosable conditions.

Principal Investigator Year	N	Subject Description	Adverse Events
Morriss, Richard 2019	161	Generalized Anxiety Disorder	4 subjects experienced the following side effects: mild headache - 2; nausea - 1; “strange feeling after use” - 1.
Morrow, Deborah 2019	91	Veterans	3 subjects withdrew due to headache.
Gong, Bing Yan 2016	74	Functional Constipation Secondary to Mental Illness	No severe side effects reported. Mild side effects included tingling in the ears at the site of the earclips - 3, earclips feeling too tight - 2, and drowsiness - 1.
Amr, Mostafa 2013	7	Bipolar Depression patients	4 patients reported mild dizziness during CES treatment, but not sufficient to discontinue.
Tan, Gabriel 2011	105	Neuropathic Pain	Alpha-Stim® CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 12; Legs, tingling. burning, electric shot in feet – 1; Spasms, leg spasms – 1; Burning in buttocks – 1; Ringing in ears – 1; Drowsy, sleepy, fell asleep, relaxing – 7; Dizzy, lightheaded, feeling crooked – 3; Nausea, stomach rolled – 1; Headache, slight headache – 2; Metallic or unusual taste in mouth – 1; Increased pain – 1. Sham CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 6; Head tingles – 1; Legs tingling, electric shot in feet – 1; Spasms, leg spasms – 2; Drowsy, sleepy, fell asleep, relaxing – 4; Dizzy, lightheaded, feeling crooked – 1; Nausea, stomach rolled – 2; Shaky – 1; Heart racing, chest pain – 2; Headache, slight headache – 3; Metallic or unusual taste in mouth – 1; Increased pain – 1. There were no serious study-related adverse events in any phase of this study (p. 292).
Rintala, Diane 2010	13	Parkinson’s Disease	Alpha-Stim® CES group: Pulsing, tickling, tingling in ears – 3; Tender ears – 1; Pins and needles sensation in bladder – 1. Sham CES group: Drowsiness – 1; Warm ears – 1; Headache – 1. No serious study-related adverse events occurred during this study (p. 4).
Eidelman, William 2009	1,000	Cigarette smokers	3 patients out of 1,000 (0.3%) were unable to tolerate the CES treatment due to vertigo (p. 83).
Mellon, Ronald R. 2009	21	Security and patrol staff of a rural jail	After the third CES session, one subject reported increased levels of agitation secondary to treatment and was removed from the study (p. 11).
Bystritsky, Alexander 2008	12	Generalized anxiety disorder	2 subjects dropped out of the study because of dizziness and one dropped out of study because of headache, (p. e3).

Strentzsch, Julie A. 2008	42	Chronic mentally ill patients in a partial hospitalization program	Alpha-Stim® CES Group: One subject from the active CES group reported increased auditory hallucinations but remained in the study with no further problems (p. 56). Sham CES Group: Two subjects from the sham group reported headaches from treatment (p. 56).
Lu, Xiao-Yan	32	Children with anxiety and depression	Three subjects occasionally felt dizziness and experienced local irritation at the electrode site. There were no serious adverse events.
Kirsch, Daniel L. 2002	500	Anxiety, depression, insomnia, pain, and stress patients	6 (1.2%) reported dizziness, and 2 (0.4%) reported nausea, both of which normally occur when the current is set too high, 3 (0.6%) reported skin irritation, 1 each (0.2%) reported, anger, a metallic taste, a heavy feeling, or intensified tinnitus (p.44).
TOTAL	**2,058**		

Adverse events reported in 12 Alpha-Stim® studies. Note: To be included in the table of studies, the study must have been done using Alpha-Stim® CES, must include a specific statement on adverse events and must be a primary source.

The total number of adverse events in the 12 Alpha-Stim® CES studies above are shown by category in the table below.

Adverse Event	CES < 1%	Sham < 1%
Ears tender, tingle, sting, itch, ear clips too tight*	21	7
Vertigo*	17	1
Drowsy, sleepy, relaxing	8	5
Headache*	5	3
Skin Irritation, earlobes	3	0
Nausea*	4	0
Agitation/Anger	2	0
Tinnitus	2	0
Metallic taste in mouth	2	1
Increased pain	1	1
Legs tingling, burning	1	1
Leg spasms	1	2
Head tingles	0	1
Pins and needles in bladder	1	0
Burning in Buttocks	1	0
Auditory hallucinations	1	0
Heavy feeling	1	0
Heart racing, chest pain	0	2
Strange feeling after use	1	0
TOTAL	**72**	**24**

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

A meta-analysis synthesizing the effect of Alpha-Stim on anxiety using the 10 key RCT studies presented above was conducted at the request of Electromedical Products International, Inc. by Dr. Larry Price from Texas State University in San Marcos, Texas. To be included in the meta-analysis, studies had to be randomized controlled experiments and rated as "good" according to the quality assessment framework described below. All 10 studies were randomized control trials with blinding of subjects and investigators to the delivery of active versus sham exposure for the treatment of anxiety. Empirical research investigations vary regarding rigor according to their conduct. The quality of studies comprising a research synthesis has a direct relationship to the validity of any conclusions arising from a synthesis. Study quality is defined as the fit between a study's goals and the study design implementation characteristics.

The quality of the studies included in the meta-analysis were evaluated using a framework and associated rubric for the assessment of the quality of a study published by Zara (2000). Scoring categories include: 0-1 limitations (rating = good); 2-4 limitations (rating = fair); 5-9 limitations (rating = limited). The table below presents Zara's framework and scoring protocol for assessing study quality. This research synthesis uses Zara's framework for the assessment of study quality.

Quality Assessment in Research Synthesis

Quality Category	Examples Items
Description (study population and intervention)	Was the study population well described?
Sampling	Did the authors specify the sampling frame or universe of selection for the study population?
Measurement (exposure)	Were the exposure variables valid measures of the intervention under study?
Measurement (outcome)	Were the outcome and other independent (predictor) variables reliable (consistent and reproducible) measures of the outcome of interest?
Data analysis	Did the authors conduct appropriate analysis by conducting statistical testing where appropriate?
Interpretation of Results: Participation	Did at least 80% of the participants complete the study?
Interpretation of Results: (comparability and bias)	Did the author(s) correct for controllable variables or institute study procedures to limit bias appropriately?
Interpretation of Results: (confounders)	Describe all potential biases or unmeasured /contextual confounders described by author(s).
Other	Other important limitations of the study not identified elsewhere?
Study Design	Concurrent comparison groups and prospective measurement of exposure and outcome.

Study outcome categories are: Good, Fair, Limited. Scoring categories include: 0-1 limitations (rating= good); 2-4 limitations (rating = fair); 5-9 limitations (rating = limited).

The advancement of scientific knowledge is based on the systematic building of one study on top of the foundation provided by other studies. The result of this process is an accumulation of knowledge that

elevates our understanding to new plateaus. Closely related to this, is replication of research findings – that the results of studies are confirmed or refuted by other researchers.

Evidence commonly comes in separate bits, and not necessarily from a single study or experiment. In contemporary science, the careful conduct of systematic reviews of the available evidence from diverse data sources is an effective and frequently used way of compiling relevant information. Meta-analyses allow for the formal, mathematical or statistical combination of information to merge data from individual investigations to a joint result. To this end, the unit of analysis in a meta-analysis is the results of studies – specifically in the form of effect sizes. Along with qualitative, often informal assessment and evaluation of the present evidence, meta-analytic methods have become a powerful tool to guide objective decision-making.

Report all relevant results, including diagrams if appropriate.

Figure 1 provides the meta-analytic results of the 10 key RCT studies on anxiety. The left side of Figure 1 provides a statistical summary of the studies, each represented by the standardized mean difference (i.e. *d*) between study groups at posttest. Due to variation in reporting of results across the 10 studies, only the difference at posttest between groups was used in calculation of the effect of Alpha-Stim CES on anxiety. To examine the magnitude of change within study groups from baseline to posttest (and other measurement points captured), please see sections 4 and 5 of this document.

The forest plot provided in Figure 1 reflects (a) the effect size *d*, (b) the variablity of each study's effect via the 95% confidence interval, and (c) the average (i.e., population estimate) effect size for all 10 studies (blue diamond). As is displayed, the *average* (population) effect for the N=10 studies was observed as [redacted](i.e., the mean anxiety level at posttest for the active group was [redacted] standard deviations *lower* than than the mean anxiety level for the sham group). An effect size of [redacted] is classified as medium (Card, 2012; Cooper et al., 2009).

Finally, the right side of Figure 1 displays the relative weight that each of the 10 studies contributed. Also informative is the width of the confidence interval. For example, the larger the sample size of an individual study, the smaller the width of the interval and the greater the precision of the effect size.

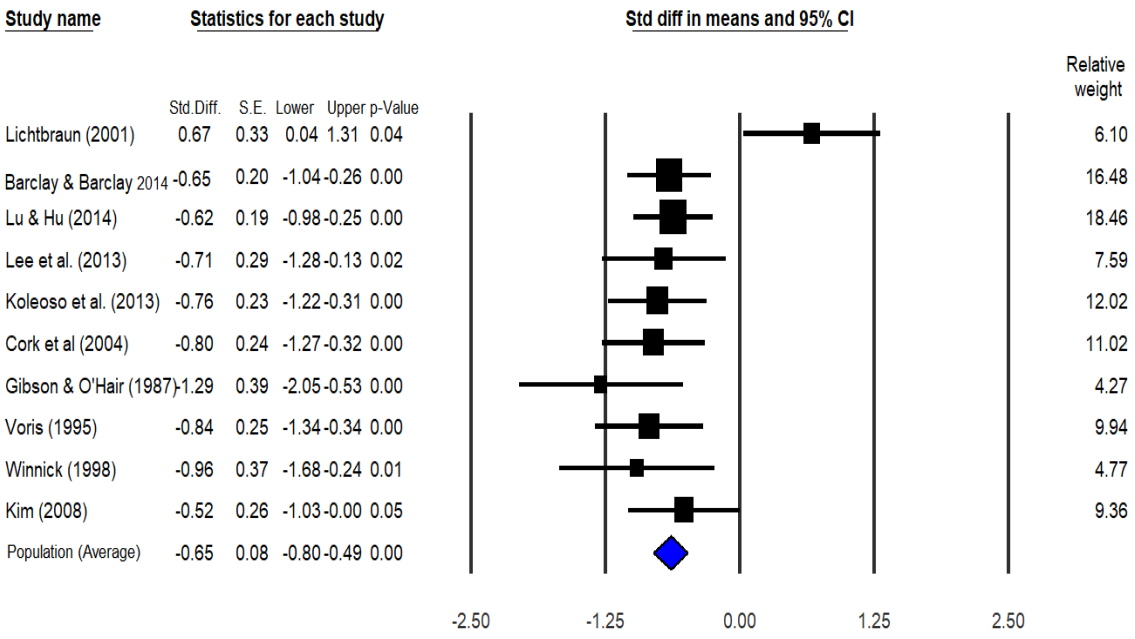


Figure 1. Summary Statistics of Effect Sizes and Forest Plot (N=10)

Table 1 displays a summary of the meta-analytic model for the N=10 studies. In meta-analytic studies, an important issue to evaluate is the heterogeneity of the studies. For example, if the heterogeneity in the studies is statistically significant, including a moderator as part of the meta-analysis may be warranted. The Q-statistic is used to test for significant heterogeneity in the effect sizes used in the analysis (i.e., that the effect sizes are more heterogeneous than expected by sampling variability alone). In Table 1, the Q-statistic is [redacted], p = [redacted], indicating that, at least some heterogeneity for the effect sizes exists. However, the Q-test does not provide information regarding the magnitude of the heterogeneity of the effect sizes – a critical issue. To evaluate the magnitude (practical) effect of the effect sizes in the N=10 meta-analysis, we turn to the I-squared value [redacted] or [redacted]%) in Table 1. The I-squared statistic is derived as the ratio of between study variance to within study variance. Studies with small sample sizes inflate the I-squared statistic. In the present meta-analysis, [redacted]% of the studies included small sample sizes (e.g., less than [redacted]subjects per group). The impact of the [redacted]sample sizes is [redacted] variability within a study thereby influencing the heterogeneity of effect sizes. A value of [redacted] ([redacted]%) is classified as a medium amount of study heterogeneity (Card, 2009, p. 189). For example, I-squared as a magnitude of study heterogeneity are: ~25% = small; ~50% = medium; ~75% = large.

In the Random-effects model, inferences are justified beyond a certain set of studies included in a specific meta-analysis to a population of potential studies of which those are representative. A comparison of the point estimates between the Fixed-effect model ([redacted]) and Random-effects model ([redacted]) are very close and tau-squared (i.e. the population variance) is relatively close to zero. In summary, the studies included in this meta-analysis (N=10) show a medium effect in favor of the [redacted] [redacted]group. Given the congruency (i.e. closeness) between the summary statistics of Fixed- and Random-effects models in Table 1, it is reasonable to also state that the research shows a medium effect in favor of the active treatment group in relative to reduction in anxiety.

Table 1. Meta-Analysis Summary Statistics

Model	Number of Studies	Point Estimate	Standard Error	Variance	Lower Limit	Upper Limit	Z-value	P-value	Q-value	P-value	I-squared	Tau Squared	Standard Error	Tau
Fixed	10	[redacted]												
Random	10													

Note. Point estimate = average standard effect, *d*, over 10 studies. Q-value = test of study heterogeneity (i.e., are the set of effect sizes homogeneous). I-squared = magnitude of study heterogeneity (~25% = small; ~50% = medium; ~75% = large).

Explain the main findings and conclusions drawn from the evidence synthesis.

The studies included in this meta-analysis span 27 years of research conducted in several different countries and with a variety of patient populations. The constant in each of the patient populations is the presence of moderate to severe emotional distress related, at least partially, to anxiety. The results of this meta-analysis demonstrate that, regardless of other limitations listed in the studies described above, when the scientific evidence from the randomized controlled trials described above is considered in its entirety, it is clear that Alpha-Stim CES treatment is effective in reducing anxiety in a variety of patient populations.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Enter text.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

There are 23 separate completed studies and one ongoing study presented for clinical evidence in this review. These studies include randomized controlled trials, open label studies, retrospective analyses, and post marketing surveys. All open label and randomized control trial studies are independent research with Alpha-Stim devices. This means Electromedical Products International, Inc. did not fund any of these studies, but did provide support to many of them through the loan of the Alpha-Stim devices utilized in the study. A meta-analysis conducted by Dr. Larry Price of Texas State University in San Marcos, Texas, of the 10 key RCT studies is also presented.

When reviewing a body of scientific evidence, such as is presented here, the gold standard is repetition of results. Taken as a whole, the clinical evidence clearly and consistently demonstrates Alpha-Stim CES is an effective and safe treatment option for people with anxiety, regardless of severity or comorbidity of medical or other psychological difficulties. Furthermore, both the clinical literature and real-world reports

indicate Alpha-Stim CES is safe, with adverse events occurring in less than 1% of cases. Adverse events are consistently mild and self-limiting and most often include dizziness, nausea, skin irritation, or headache, which are indications the device was set too high for the user. When compared with information regarding safety and effectiveness of mainline treatment options for anxiety, especially medications, the data clearly shows Alpha-Stim CES has much fewer and milder adverse effects and is at least as, if not more, effective in reducing anxiety.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

Any individual study has limitations. No conclusions regarding the effectiveness or safety of a treatment option should ever be drawn based on just one or two studies, no matter how well-designed. However, when a treatment option can produce numerous studies spanning decades, as is presented in the 24 studies detailed above dating back to 1987, as well as evidence from thousands of patients utilizing it in real-world situations, then conclusions about that treatment option can be made with confidence. The data detailed above, including studies conducted in a variety of methods, real-world data, and adverse event reports from both patients and clinical studies, repeatedly demonstrate that Alpha-Stim CES is a very safe and effective treatment option for people suffering from the broad spectrum of anxiety, up to and including diagnosable anxiety disorders.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The submitted studies investigated the effects of Alpha-Stim CES on a wide variety of patients from many countries, age groups, medical and psychological disorders. Thus, one can be confident the patients in the submitted studies are similar to patients who would be receiving care in the UK NHS. Anxiety, and anxiety disorders, do not occur in a vacuum, and can be exacerbated by, and itself exacerbate, other conditions and life stressors. By presenting evidence of patients with chronic medical conditions, in stressful careers or life situations, as well as with diagnosable anxiety disorders, we have demonstrated that Alpha-Stim CES is a safe and effective treatment option for patients experiencing the entire spectrum of anxiety, from situational anxiety to chronic, severe, diagnosable anxiety.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The clinical and real-world evidence presented in this review indicate Alpha-Stim CES is an appropriate, safe, and effective treatment option for patients struggling with anxiety, regardless of gender, age, race, medical condition, or comorbid psychological condition. The only contraindications for use of Alpha-Stim are:

1) Presence of an implanted electrical device that cannot be turned off, such as a cochlear implant, pacemaker, or defibrillator.
2) Pregnancy

These two conditions are listed in the studies as exclusion criteria for all of the studies detailed above.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The strength of the clinical evidence for this technology is its scope. 24 studies, including 13 randomized controlled trials, spanning 32 years and more than 3,000 participants, have been presented, and all studies demonstrate that this technology effectively and safely reduces anxiety. As stated above, while RCTs are the “gold standard” for a single clinical trial, the gold standard when evaluating a body of scientific evidence is repetition. If all the research, regardless of method used, repeatedly has similar results, and those results are similar to real-world data from clinical use, then one can have the utmost confidence in the results. Therefore, given the consistency of the results of the studies and information from patients using the device clinically, it is obvious Alpha-Stim CES is safe and effective in treating anxiety.

9 References

Please include all references below using NICE's standard referencing style.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	March 9, 2020
Date span of search:	January 1981 to March 2020
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
Searched Google Scholar, PubMed, PubMed Central Search terms were “anxiety” “Alpha-Stim,” “CES,” “electrotherapy,” “cranial electrotherapy stimulation.” The terms anxiety, electrotherapy, CES, and cranial electrotherapy stimulation were paired with the term “Alpha-Stim” to limit findings to the device in question.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
www.alpha-stim.com.	
Inclusion and exclusion criteria:	
Exclusion criteria included CES devices that are not Alpha-Stim. Inclusion criteria were studies utilizing Alpha-Stim technology.	
Data abstraction strategy:	
Screened abstracts of returned articles to investigate for inclusion or exclusion criteria. Articles that were not excluded when the abstract was screened were read more carefully for inclusion or exclusion.	

Excluded studies

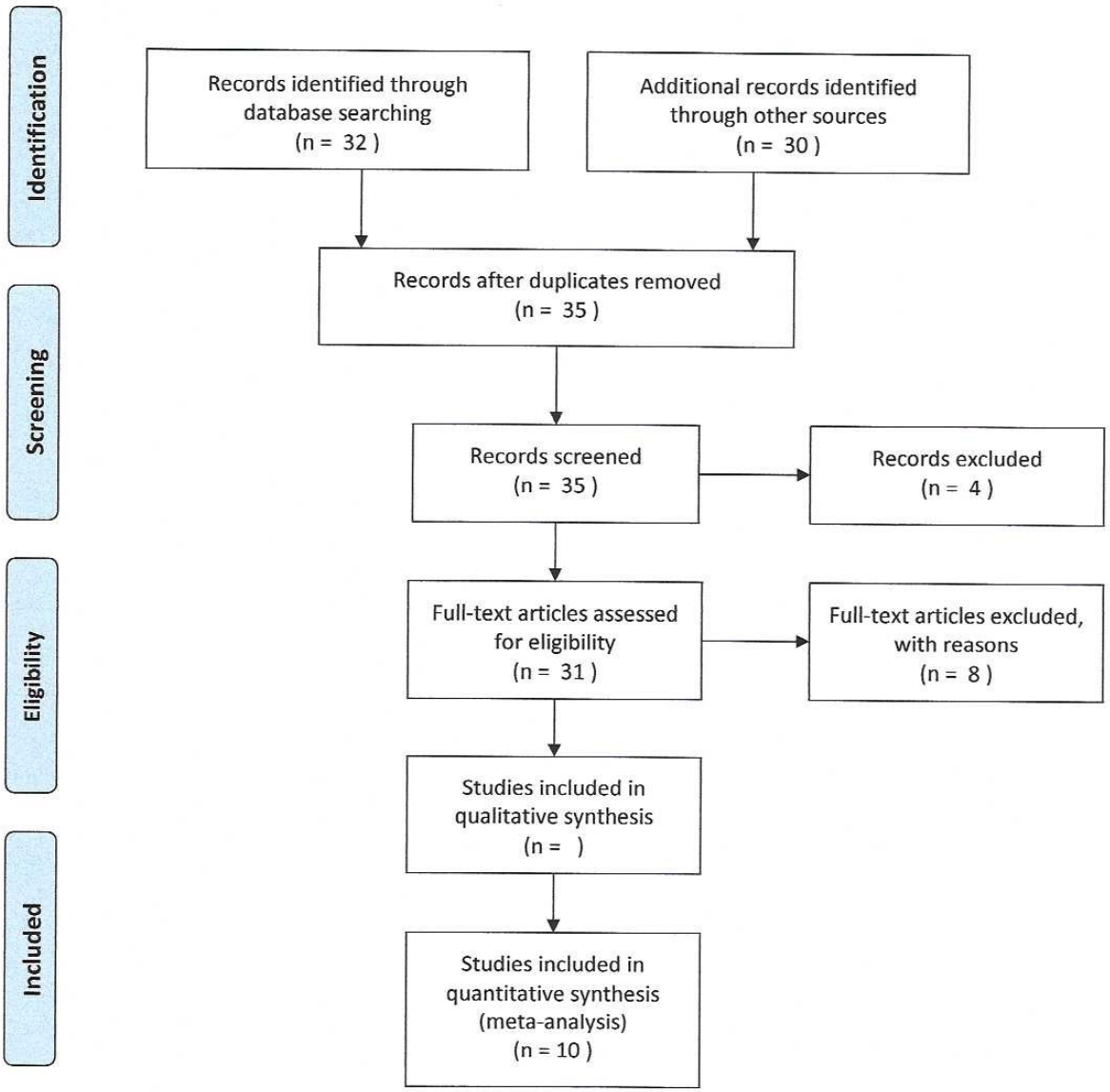
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Rickabaugh et al. (2016)	Retrospective Alpha-Stim CES	Poor study design	This unpublished study altered its treatment requirements and lumped several dependent variables, including anxiety, to report a reduction in general distress.
Mellen et al. (2016)	Open Label Alpha Stim CES	Small sample size (N=10)	This study demonstrates the effectiveness of using Alpha-Stim in a non-clinical setting to treat anxiety in women who are victims of domestic violence living in a shelter. However, the sample size, which was by necessity small, given the transient nature of this population, was too small to be considered in this review.
Lyon et al. (2015)	RCT Alpha-Stim CES	Participants in the study were women beginning treatment for breast cancer. Mean anxiety levels were mild at beginning of study, and therefore not clinically significant to include in a review on anxiety disorders.	Although this is a well-designed study with a large sample size, the initial anxiety levels were low, indicating mild distress, at best, at the onset of the study. Therefore, the study is not appropriate for inclusion in a review of Alpha-Stim treatment for clinical levels of anxiety.
Hill (2015)	RCT Alpha-Stim CES	Small sample size (N=17)	This thesis completed as part of the requirements for a Master's Degree utilized college students without a diagnosed anxiety disorder and had a sample size that was too small to be considered for inclusion in this review.
Bystritsky et al. (2008)	Open label Alpha-Stim CES	Small sample size (N=12)	This study is excellent, well-designed with significant results. However, its small

			sample size was too small to be included in this review.
Strentzsch (2008)	RCT Alpha-Stim CES	Of the 42 psychiatric patients in this study, only 5 had an anxiety diagnosis.	While this study does show significant decreases in state anxiety among patients with severe mental illness, there were insufficient participants with a primary anxiety disorder to be included in this review.
Chen et al. (2007)	RCT Alpha-Stim CES	This study examined treatment of Alpha-Stim in children ages 8-16 diagnosed with Mixed Anxiety and Depressive Disorder (MAD) in China.	This is a well-designed, strong study, but the population is outside the scope being considered for this review.
Lu et al. (2006)	RCT Alpha-Stim CES	This study examined treatment of Alpha-Stim in children ages 9-17 diagnosed with Mixed Anxiety and Depressive Disorder (MAD) in China.	This is a well-designed, strong study, but the population is outside the scope being considered for this review.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

March 9, 2020 Literature search Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Structured abstracts for unpublished studies

Study title and authors: Price LR (2013) Alpha-Stim® user effectiveness survey abstracts in the 2013 supplement information to the CDRH for Alpha-Stim® CES, August 5th 2013.
Introduction: Self-report data on the perceived effectiveness of Alpha-Stim® was acquired from 2,861 respondents through a mail survey. Data collection occurred between January 2007 and July 2013. The primary focus of the survey was to acquire information regarding the effectiveness of using Alpha-Stim® for the treatment of anxiety, insomnia, depression, pain and PTSD. Eighteen percent (513) of the respondents exhibited nonresponse on at least one of the questions, diagnosis or improvement and were not included in the analyses. The final sample size used in the descriptive analyses after screening the data for overt errors in coding, aberrant or out of range values and item nonresponse was N=2,348, providing a useable response rate of 82% for the diagnosis and improvement questions. One reason for the excellent response rate was that the user survey was included on the warranty card in the Alpha-Stim® device kit with instructions to complete the survey and return the warranty card after using the Alpha-Stim® device for at least 30 days.
Objectives: This post marketing survey was conducted as part of the requirements for Electromedical Products International, Inc. to monitor the safety and effectiveness of Alpha-Stim technology.
Methods: Post marketing survey
Results: 99.9% of respondents stated Alpha-Stim CES was safe and effective in treating their symptoms. 36% of respondents treating anxiety disorders stated Alpha-Stim was the most effective treatment method they had tried. 82.9% of respondents indicated improvement in their anxiety symptoms, and 89.7% of respondents with PTSD indicated improvement in their symptoms.
Conclusion: The majority of patients responding to the survey indication Alpha-Stim technology is very safe and effective in treating anxiety, depression, insomnia, and pain.
Article status and expected publication: This post marketing survey has not been published, but is readily available on the Alpha-Stim website (www.alpha-stim.com).

Study title and authors: Voris MD (1995) An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among psychiatric patients, impulse control parolees and pedophiles.
Introduction: There are a number of available treatment modalities for anxiety, including psychotropic medication, cognitive restructuring, and ongoing relaxation training and various meditation techniques. However, there are a number of drawbacks to these traditional treatment techniques. Anti-anxiety medications tend to be addictive and have significant side effects. The amount of intellectual and personal discipline necessary to maintain an ongoing practice of biofeedback, meditation, and relaxation is often lacking in patients who appear in the clinician's office. An alternative that has been demonstrated to be effective is cranial electrotherapy stimulation (CES).
Objectives: To evaluate the effect of a single treatment of CES on anxiety in outpatient psychiatric patients when compared to sham treatment under the same experimental conditions in subjects meeting the inclusion and exclusion criteria.
Methods: This was an IRB approved randomized, sham controlled, double-blind study in which subjects received either active CES or sham cranial electrotherapy stimulation for one 20-minute treatment during their regular group therapy session. There was also a usual care control group. The subjects, investigators, statistician and staff were all masked as to the identity of the device.
Results: The active CES group had significantly lower anxiety scores on the State Anxiety Inventory (SAI) compared to sham group (p=.0001, d=-1.60) and control groups. The active CES group had significantly lower scores on EMG (p=.0001, d=-1.08) and increased scores on finger temperature (p=.0141. d=.50) than sham and control groups, indicating less anxiety. The three figures below show results of statistical analyses of outcome measures for the active group compared to the sham and control groups.

Conclusion: There was clear anxiety reduction between the active and sham or control treatment groups. The investigators caution against replacing human interaction contact (therapy) with CES, but state the technology can be utilized to enhance treatment.
Article status and expected publication: This study was not published because the author passed away shortly after completing the study.

Appendix B: Search strategy for adverse events

Date search conducted:	March 27, 2020
Date span of search:	January 1, 1980 to March 27, 2020
List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.	
The MHRA and FDA MDR and MAUDE databases were searched, using the search terms “Alpha-Stim” in the device fields of both databases. No records were returned on the MHRA databases. Only the two records described in Section 6 above were returned.	
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):	
Electromedical Products International, Inc. maintains records on adverse events reported both in clinical data and from customers. These records are updated with each reported adverse event in the clinical literature or from customers. None of the studies identified in the literature searches described in Appendix A resulted in additional adverse effects listed other than the ones in the EPII records.	
Inclusion and exclusion criteria:	
All adverse reactions from national databases and from EPII records have been included in this report. None were excluded.	
Data abstraction strategy:	
The two cases from the MAURA databases were read, then copied into this review along with the URL to facilitate future access to those reports. All data obtained by searching the national and company databases were utilized in this review.	

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

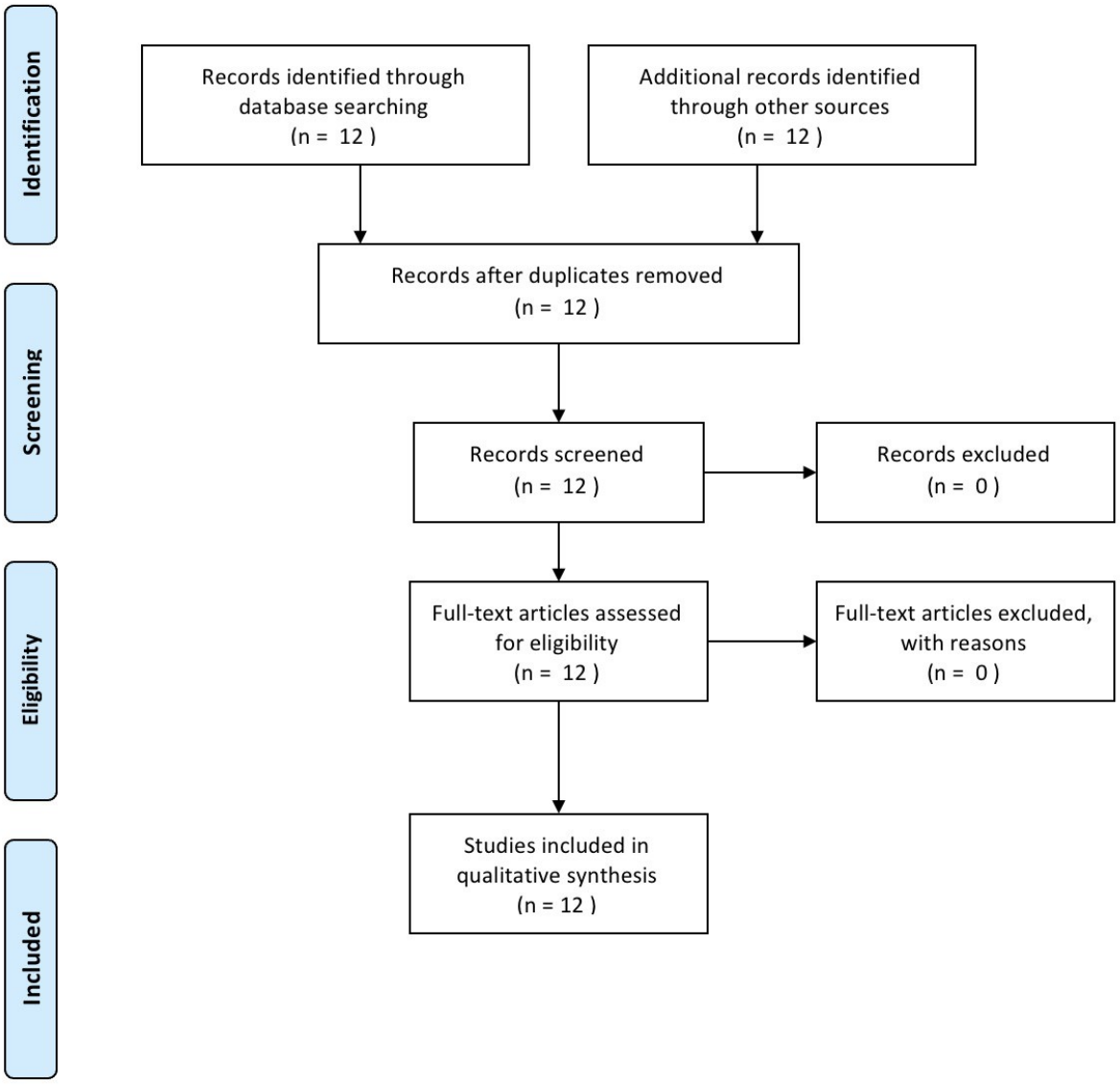
Study	Design and intervention(s)	Details of adverse events	Company comments
Morris (2019)	Open label Alpha-Stim CES	mild headache - 2; nausea - 1; "strange feeling after use" - 1.	All reported adverse events were mild. Headaches and nausea are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Morrow (2019)	Open Label Alpha-Stim CES	Headache - 3	All reported adverse events were mild. Headaches are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Gong (2016)	Open Label Alpha-Stim CES	Tingling in the ears at the site of the earclips – 3; earclips feeling too tight – 2; drowsiness - 1	All reported adverse events were mild. Drowsiness is known possible effect and usually occurs when treatment is stopped too soon. Continuing treatment for a few additional minutes will alleviate the feeling of drowsiness. Feelings of "tingling" at the site of the earclips is a normal aspect of CES treatment and is not harmful.
Amr (2013)	Open Label Alpha-Stim CES	Mild dizziness - 4	All reported adverse events were mild. Dizziness is a known possible effect and usually occur when the current is set too high for the patient. It is usually are mild and self-limiting.
Tan (2011)	RCT Alpha-Stim CES	Alpha-Stim® CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 12; Legs, tingling. burning, electric shot in feet – 1; Spasms, leg spasms – 1; Burning in buttocks – 1; Ringing in ears – 1; Drowsy, sleepy, fell asleep, relaxing – 7; Dizzy, lightheaded, feeling crooked – 3; Nausea, stomach rolled – 1; Headache, slight headache – 2; Metallic or unusual taste in mouth – 1; Increased pain – 1. Sham CES group: Ears pulse, tingle, sting, itch, ear clips too tight – 6; Head tingles – 1; Legs tingling, electric shot in feet – 1; Spasms, leg spasms – 2;	All reported adverse events were mild. Tingling at the site of the earclips is a normal aspect of CES treatment and is not harmful. Headache, nausea, dizziness and drowsiness are known possible effects and usually occur when the current is set too high for the patient. The sensations of burning, tingling, or spasms is likely attributable to the population studied and the aim of the study to treat neuropathic pain with CES.

		Drowsy, sleepy, fell asleep, relaxing – 4; Dizzy, lightheaded, feeling crooked – 1; Nausea, stomach rolled – 2; Shaky – 1; Heart racing, chest pain – 2; Headache, slight headache – 3; Metallic or unusual taste in mouth – 1; Increased pain – 1.	
Rintala (2010)	RCT Alpha-Stim CES	Alpha-Stim® CES group: Pulsing, tickling, tingling in ears – 3; Tender ears – 1; Pins and needles sensation in bladder – 1. Sham CES group: Drowsiness – 1; Warm ears – 1; Headache – 1.	All reported adverse events were mild. Pulsing and tingling sensation at the earclip site is a normal aspect of CES treatment and is not harmful. Participants were being treated for Parkinson's Disease, which may account for "pins and needles sensation in bladder" reported by one participant.
Eidelman (2009)	Open label Alpha-Stim CES	Vertigo - 3	All reported adverse events were mild. Vertigo is a known possible effect and usually occurs when the current is set too high for the patient.
Mellen (2009)	RCT Alpha-Stim CES	Agitation – 1	The reported agitation was mild and self-limiting. Although extremely rare, this type of paradoxical effect is a known possibility of CES treatment.
Bystritsky (2008)	Open label Alpha-Stim CES	Dizziness – 2; headache - 1	All reported adverse events were mild. Headaches and dizziness are known possible effects and usually occur when the current is set too high for the patient. They are mild and self-limiting.
Strentzch (2008)	RCT Alpha-Stim CES	Alpha-Stim® CES Group: One subject from the active CES group reported increased auditory hallucinations but remained in the study with no further problems (p. 56). Sham CES Group: Two subjects from the sham group reported headaches from treatment (p. 56).	All reported adverse events were mild. The reported headaches were in the sham group and therefore not related to CES treatment. The increased hallucinations occurred in a psychiatric patient with a history of hallucinations and unlikely to be related to the CES treatment.
Lu (2005)	Open label Alpha-Stim CES	Dizziness and some irritation at site of earclips - 3	All reported adverse events were mild. Dizziness and skin irritation at the electrode site are known possible effects and usually occur

			when the current is set too high for the patient. They are mild and self-limiting.
Kirsch (2002)	Survey Alpha-Stim CES	Dizziness – 6; nausea – 2; skin irritation – 3; heavy feeling – 1; anger – 1; metallic taste – 1; intensified tinnitus – 1.	All reported adverse events were mild. Nausea, skin irritation, and dizziness are known possible effects and usually occur when the current is set too high for the patient. A heavy feeling is also a known effect and can occur when treatment is stopped too soon. Paradoxical effects such as anger and increased tinnitus are extremely rare, but known effects that are mild and self-limiting.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Adverse events in published studies search Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

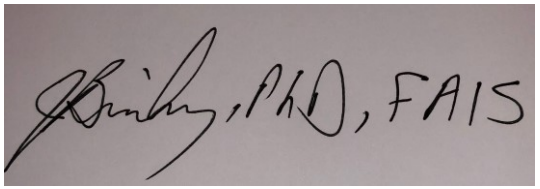
Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
37,48, & 55	☐ Commercial in confidence ☒ Academic in confidence	Ongoing clinical study investigating the effectiveness of Alpha-Stim in the treatment of anxiety and depression among patients in a primary care setting requesting mental health care.	Study should be completed later this year and submitted for publication in late 2020 or early 2021.
Details	Dr. Royal provided preliminary results of anxiety treatment with Alpha-Stim in some of his participants. The study is ongoing and will include comparisons between patients receiving usual care and patients in treatment with Alpha-Stim.		
84-87	☐ Commercial in confidence ☒ Academic in confidence	Unpublished meta-analysis of anxiety studies.	Meta-analysis will be submitted for publication as part of a review on the effectiveness of Alpha-Stim treatment of anxiety and depression by late 2020.
Details	The meta-analysis presented as part of this submission was conducted to synthesize the studies conducted with Alpha-Stim in the treatment of anxiety to demonstrate the strength of the data as a whole, as well as individually as presented in this submission. Similar meta-analyses have been conducted on studies with Alpha-Stim treating depression as part of a review of that research. The reviews of the research on Alpha-Stim in the treatment of anxiety and depression will be submitted for publication later this year.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	April 28, 2020
Print:	Josh Briley, Ph.D., FAIS	**Role / organisation:**	Science and Education Director Electromedical Products International, Inc.
Contact email:	josh@epii.com		

Medical technologies guidance

MT477 – Alpha-Stim AID for Anxiety

Company evidence submission

Part 2: Economic evidence

Company name	Electromedical Products International, Inc.
Submission date	June 11, 2020
Contains confidential information	No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		1
Number of studies identified as being relevant to the decision problem.		1
Of the relevant studies identified:	Number of published studies.	1
	Number of abstracts.	0
	Number of ongoing studies.	1

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
Journal of Affective Disorders - Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder	Morriss, R., Xydopoulos, G., Craven, M., Price, L., & Fordham, R. 2019, UK	Consecutive sample of eligible patients with GAD waiting for individual cognitive behaviour therapy (CBT) selected from two publicly funded services in England.	Intervention 60 min per day Alpha-Stim CES for 6–12 weeks. The main comparators / CBT implementation models were the 'Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, the 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, and a model suggested by experts as the standard practice including 8 low intensity iCBT sessions	Alpha-Stim is costing £ 70 per patient per duration of treatment Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 per duration of treatment per patient, The 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing £1863.57 Standard Practice model costing £887.68	The primary outcome is the proportion of participants who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7 since IAPT services are paid according to the proportion of patients who reach this threshold after treatment in their service. Other key outcomes are the proportion of cases who meet a clinically important ("reliable improvement") 5-point improvement on the GAD-7 at 12 and 24 weeks The hypothesis tested in the HE model was that adding CES as a second-line treatment in the pathway will eliminate, for the proportion of patients who respond to CES, the need for the more expensive iCBT leading to cost saving. The results of the health economics decision tree model populated with the costs and probabilities for the 8 sessions standard care model of CBT yielded the following results. The costs and responses are presented for a cohort of 1000 patients. CES provided a saving of−£540,878(95%CI [−£648,692, −£327,117]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [141.03, 227.82]). Using the "Clark and Wells model" of iCBT as comparator, CES provided a saving of −£1,637,410 (95% CIs −£1,914,463, −£1,175,437]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [141.58, 226.12]). With the Heimberg Model as a comparator, CES provided a saving of −£1,212,463 (95% CI −£1,429,369, −£843,394]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [140.79., 227.71]).	A probabilistic sensitivity analysis (PSA) was undertaken on cost of treatment, probability of response and utilisation of response parameters, 2016). In addition, a one-way deterministic threshold analysis was performed on cost to find the price at which the intervention would no longer be cost saving. Probabilistic Sensitivity Analysis (PSA) is a technique used in economic modelling that allows the quantification of the level of confidence in the output parameters of the analysis, in relation to the uncertainty in the model inputs.

A Work Project, presented as part of the requirements for the Award of a Master's degree in Management from the Nova School of Business and Economics.	NEJC HLADNIK Nova School of Business and Economics Slovenia 2020	Real patient data with GAD waiting for individual cognitive behaviour therapy obtained from moj.zzzs.si portal ("my.zzzs.si"), a user accessible portal of the National Health Insurance Institute	To determine the cost impact of introducing CES into the care pathway for mental disorders in Slovenia, as a second-line treatment instead of or prior to a second-line iCBT, a cost minimization analysis was undertaken using a health economics model decision tree	For each 1-hour session, 3 distinctive service codes are used (96190, 11305 and 02003/05), which checked against the latest ZZZS's code register (ZZZS 2020b), and the official 2020 price list (ZD Koper 2019) results in a total cost of 48.68 €. For the medical device, the total cost was set at 70 € ex./VAT per a 12-week treatment, including the supplier's reimbursement, consumables, postage and 13.7 € worth of additional specialist time, valued through service codes (11305 for treatment continuation, 02003/05 for examination and 91100 for making a prescription). For non-responders to second-line iCBT, a further course of the same number of iCBT sessions would follow (8 and 10 sessions were compared), with the same/constant remission probability. For non-responders to second-line CES, up to two further courses of iCBT were included in the decision tree. Nevertheless, results are provided also for the case if only 1 or none further iCBT courses followed.	When Alpha-Stim is compared to 8-session iCBT solely on the first round's head-to-head basis, 1,000 patients could be treated without therapists for 319,400 € less, at an incremental loss of 70 patients that do not respond to treatment Next, if Alpha-Stim is introduced as a second-line intervention prior to a double round second-line iCBT, a cost reduction of 198 € per patient is observed. With 1,000 patients, a cost saving of 198,000 € is achieved, with 99 more patients responding. The threshold price is 268 €. Finally, if Alpha-Stim is used instead of just the 1st-legged iCBT, an additional incremental saving of 94.000 € is observed but at an incremental cost of 131 not responding. The threshold price is at 362 €. When Alpha-Stim is compared to a 10-session iCBT solely on the first round's head-to-head basis, 1.000 patients could be treated without therapists for 416.800 € less, at an incremental loss of 70 patients (Fig. 2). Next, if Alpha-Stim is introduced as a second-line intervention prior to a double round second-line iCBT, a cost reduction of 265 € per patient is observed. In a pool of 1.000 patients, a cost saving of 265 thousand € is achieved, with 99 more patients responding. The threshold price is for this case 335 €. Finally, if Alpha-Stim is used instead of just the 1st-legged iCBT, an additional incremental saving of 118 thousand € is observed but 19 at an incremental cost of 131 patients not responding. The threshold price is for this case at 452 € per treatment.	

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder	
What are main differences in resource use and clinical outcomes between the technologies?	Alpha-Stim is costing £70 per patient per duration of treatment (60 min per day Alpha-Stim CES for 6–12 weeks). Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 per duration of treatment per patient. The 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing £1863.57. Standard Practice model that includes 8 low intensity iCBT sessions costing £887.68.
How are the findings relevant to the decision problem?	The findings prove that Alpha-Stim can be as effective as iCBT reducing the cost for more expensive interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Alpha-Stim reduces the need for individual CBT presenting significant cost savings.
Will any information from this study be used in the economic model?	Yes, the response rates and service unit costs.
What cost analysis was done in the study? Please explain the results.	This was a cost minimisation study showing that Alpha-Stim reduces the need for individual CBT presenting significant cost savings.
What are the limitations of this evidence?	Participants were not randomised and there was no control group. Only 48 (29.9%) participants completed every assessment thus control group parameters had to be derived from a limited sample of studies. Another limitation of the study was that the sample lacked ethnic diversity. The sample was drawn from all ages although there were greater proportions of younger and middle-aged participants in the study, reflecting the composition of age groups in routine IAPT NHS services. As expected, the vast majority of patients with GAD were female. There was a broad representation of education, marital status and employment status reflecting the age composition of the sample.
How was the study funded?	The study was supported by Electromedical Products International, Inc., by loaning devices for

	the study. The chief investigator's time was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East Midlands and Nottingham NIHR Biomedical Research Centre. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

A Work Project, presented as part of the requirements for the Award of a Master's degree in Management from the Nova School of Business and Economics	
What are main differences in resource use and clinical outcomes between the technologies?	For the medical device, the total cost was set at 70 € ex./VAT per a 12-week treatment, including the supplier's reimbursement, consumables, postage and 13.7 € worth of additional specialist time, valued through service codes (11305 for treatment continuation, 02003/05 for examination and 91100 for making a prescription). For non-responders to second-line iCBT, a further course of the same number of iCBT sessions would follow (8 and 10 sessions were compared), with the same/constant remission probability. For non-responders to second-line CES, up to two further courses of iCBT were included in the decision tree. Nevertheless, results are provided also for the case if only 1 or none further iCBT courses followed.
How are the findings relevant to the decision problem?	The findings demonstrate that Alpha-Stim can be as effective as iCBT reducing the cost for more expensive interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Alpha-Stim reduces the need for individual CBT presenting significant cost savings.
Will any information from this study be used in the economic model?	Yes, the response rates.
What cost analysis was done in the study? Please explain the results.	This was a cost minimisation study showing that Alpha-Stim reduces the need for individual CBT presenting significant cost savings.
What are the limitations of this evidence?	Participants were not randomised and there was no control group. No sensitivity analysis presented.
How was the study funded?	The study was completed as part of the academic requirements for a Master's Degree.

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Consecutive sample of eligible patients with GAD waiting for individual cognitive behaviour therapy (CBT) selected from two publicly funded services in England Inclusion/exclusion criteria 1. A score of 8 or more on GAD-7 scale, a 7-item self-rated measure of symptoms of generalised anxiety disorder (Spitzer et al., 2006), because nationally IAPT services determined that further treatment should be offered after full or guided computerised self-management or bibliotherapy if a person scores above the threshold for remission i.e. a total score of 8 or more. 2. A clinical diagnosis of generalised anxiety disorder alone or in combination with a comorbid depression or other anxiety disorder e.g. obsessive-compulsive disorder or physical health morbidity. Excluded was a diagnosis of any other mental disorder e.g. substance use disorder, eating disorder, bipolar disorder, non-affective psychosis. In keeping with an implementation study the diagnostic information used for the inclusion and exclusion criteria were made on clinical grounds without using any standardised psychiatric interviews by clinically qualified mental health professionals independently of the research team. 3. On waiting list for individual CBT (high intensity psychological intervention). 4. Does not require urgent clinical care. 5. If female not known to be pregnant. 6. Implantation with a pacemaker or an implantable cardioverter device (ICD) are exclusions. 7. Gives informed written and oral consent to the study. 8. Agrees to return Alpha-Stim equipment at the end of the study. Being on medication did not lead to exclusion.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Alpha-Stim's cranial electrotherapy stimulation (CES) technology in second line treatment was compared against the currently implemented second line iCBT not taking into account medication as a comparator. Initially the model was built following comparing Alpha-Stim against iCBT alone, without mention on medication. Medication wasn't therefore controlled for, so there may well have been a mix of those on and not on any relevant anxiety medications. We can assume therefore that the data of the response to Alpha-Stim presents a representative mix of patients both on and off medication The main comparators / CBT implementation models were the 'Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 per duration of treatment per patient, the 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing

£1863.57 per duration of treatment per patient and a model suggested by experts as the standard practice including 8 low intensity iCBT sessions

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

In order to determine the cost impact of introducing CES into the pathway as a second-line treatment instead of or prior to individual CBT (iCBT), a cost minimisation analysis was undertaken using a health economic (HE) model decision tree. In both branches of the HE model the patient population was non-responders to low-intensity guided or full computerised self-help or bibliotherapy given as the first line treatment. The decision tree was populated with the probabilities of response to second line CES treatment from the study versus second line iCBT with the remission rate of 54.2% from Gyani *et al* (2013) which is the average remission rate between guided and full self-help groups in that study. In addition, the same probability of outcome from subsequent iCBT sessions given to non-responders in both arms was modelled as in the current pathway (treatment as usual) such that for non-responders to second line iCBT a further course of the same number of iCBT sessions would follow. For non-responders to second line CES up to two further courses of iCBT were included in the decision tree. In all cases successful response was measured by the achievement of the GAD-7 threshold of remission as used in the IAPT programme (Richards & Borglin, 2011). Neither a cost-utility analysis nor a cost consequences analysis was employed because the study did not have a comparator for outcomes although EQ-5D results are reported here separately for Alpha-Stim CES treatment. The hypothesis tested in the HE model was that adding CES as a second-line treatment in the pathway will eliminate, for the proportion of patients who respond to CES, the need for the more expensive iCBT leading to cost savings.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Probability of Response to Individual CBT 0.542	Based on published literature	Gyani, A. et. Al 2013
Probability of Response to Alpha-Stim 0.47	Based on evidence provided by the company	Text
Patients per Alpha-Stim life expectancy – 5 patients	Based on evidence provided by the company	Text
Per patient cost of Alpha-Stim - £70	Based on evidence provided by the company	Text

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Response to second line iCBT-	Gyani, A. et al. 2013	0.542	0.49 – 0.59	Used to calculate the population response and in the sensitivity analysis modelled under a Beta distribution
Response to Alpha-Stim	The Microcurrent Site	0.47	0.38-0.48	Used to calculate the population response and in the sensitivity analysis modelled under a Beta distribution
Models of CBT sessions	NICE, Griffiths and Steen, 2013	The Clark and Wells Model 14 high intensity sessions The Heimberg Model- 15 low intensity sessions and one high intensity Standard Practice – 8 high and 8 low intensity sessions	N/A	Used in the calculation of the implementation costs of iCBT

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

N/A

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	The model uses a decision-tree structure with a 6-month time horizon	The time horizon of the model is reflecting the expected duration of generalised anxiety disorder response	N/A
Discount rate	N/A	Given the short time horizon of the model, costs and outcomes are not discounted.	Text
Perspective (NHS/PSS)	NHS	This is a technology envisaged to be adopted by NHS services	Text
Cycle length	1 Cycle	The model uses a decision-tree structure	Text
Transition probabilities	Text	Text	Text
Health states	Response to iCBT / No response t ICBT Response to Alpha-Stim / No response to Alpha-Stim	According to the aims of the study	Text
Sources of unit costs	Radhakrishnan et al, 2013	Analytic breakdown of the cost of high and low intensity CBT sessions	Text

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

Patients that do not respond to Alpha-Stim they will go to a first round of ICBT followed by a second round if they do not respond as well. If patients respond to the first round of Alpha-Stim they are considered treated.

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Alpha-Stim CES cost per treatment was a manufacturer estimate from the unit cost of the device of £450.00 (excluding valued added tax) with a utilisation of 15 patients over an average product lifetime of 3 years (based on 10-week sole use per patient). It allowed for losses with respect to the quoted 5-year warranty that was estimated to reduce average product lifetime by 2 years. Additional therapist time, postage and consumables was estimated at £40, yielding £70 per duration of the treatment per patient.

If the list price is not used in the model, provide the price used and a justification for the difference.

The per patient cost used in the model is £70 which is not the list price of the device. The recommended treatment duration for each patient using the Alpha-Stim AID is 8 weeks, therefore each device can be used by multiple NHS patients during the 5 year warranty period, providing justification for the difference.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Overall treatment costs were computed for 8 sessions of 60 min iCBT, as in the 'standard of care' model, yielding a total cost of £887.68. For comparison, the model was also constructed with alternative choices of two additional more expensive iCBT regimes: ie. the 'Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 in total and the 'Heimberg model' with just one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing £1863.57 in total. The CBT session models where derived from NICE guidelines on Social Anxiety Disorder recognition, assessment and treatment § 6.13.2

PSSRU 2013 reported costs between £21.98 (computerised CBT) and £141.41 (CBT/IAPT) for the treatment of anxiety and depression. For a more analytic estimation of sessions and cost per sessions time costs were derived for CBT from Radhakrishnan *et al* (2013) for 60 or 90 min of iCBT (£98.59 or £ 176.97 per session) uplifted from 2010 to 2016 prices using the appropriate ratio of 1.09 yielding £ £110.96 and £199.17 respectively.

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

All the data used in the final version of the model referred to resource data for the NHS in England.

The main CBT implementation models were the 'Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 in total and the 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing £1863.57 in total.

The CBT session models where derived from NICE guidelines on Social Anxiety Disorder recognition, assessment and treatment § 6.13.2

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Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

The cost of the device per patient is calculated to be £70 The prevalence of GAD in UK is 5.9% according to Baker, C., & House of Commons Library. (2020). So in total it will be required £272,580,000 to cover the need of the whole population

Baker, C., & House of Commons Library. (2020). Mental health statistics: prevalence, services and funding in England. House of Commons Library, (6988), 29. Retrieved from https://researchbriefings.parliament.uk/ResearchBriefing/Summary/SN06988

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

N/A

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

N/A

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

	Technology costs	**Comparator 1 costs** **iCBT The Clark and Wells Model**	**Comparator 2 costs** **The Heimberg Model**	**Comparator 3 costs** **Standard of care**	**Difference in resource use costs (technology vs comparator 1)**	**Difference in resource use costs (technology vs comparator 2)**	**Difference in resource use costs (technology vs comparator 3)**
Cost of resource use to implement technology	£70 per patient	£ 2,788.43 Per patient	£1863.57	£887.68	- £ 2,788.43	-£ 1,793.57	-£817.68
Cost of resource use associated with patient outcomes	N/A	N/A	N/A		N/A	N/A	
Cost of resource use associated with	N/A	N/A	N/A		N/A	N/A	

system outcomes							
Total costs	N/A	N/A	N/A		N/A	N/A	

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

N/A

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
Adverse event 1	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
Adverse event 2	Technology	Text	Text
	Staff	Text	Text
	Hospital costs	Text	Text
	[Other items]	Text	Text
	Total	Text	Text
[Add more rows as needed]			

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

None

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Potential of the intervention to release time from consultant psychologist to cover the needs of populations with other conditions Reduced medication costs in Primary Care and reduced cost in treating complications of medication use such as overdose Reduced use of healthcare resources, for instance reducing GP visits or outpatient visits.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	£30 per patient	The Microcurrent Site Ltd.
Consumables per year (if applicable) and over lifetime of device	£10 per patient	The Microcurrent Site Ltd.
Maintenance cost per year and over lifetime of device	N/A	N/A
Training cost over lifetime of device	£5 per patient	The Microcurrent Site Ltd.
Other costs per year and over lifetime of device	£25 per patient	The Microcurrent Site Ltd.
Total cost per treatment/patient over lifetime of device	£70 per patient	The Microcurrent Site Ltd.

Table 8 Total costs for the comparator in the model

Description	Cost	Source
Cost per treatment/patient over lifetime of device	£ 2,788.43 Per patient - The Clark and Wells Model £1863.57 - The Heimberg Model £887.68 - Standard of Practice	NICE guidelines on Social anxiety disorder recognition, assessment and treatment § 6.13.2 Radhakrishnan et al (2013)
Consumables per year (if applicable) and over lifetime of device	N/A	N/A
Maintenance cost per year and over lifetime of device	N/A	N/A
Training cost over lifetime of device	N/A	N/A
Other costs per year and over lifetime of device	N/A	N/A
Total cost per treatment/patient over lifetime of device	£2,788.43 Per patient - The Clark and Wells Model £1863.57 - The Heimberg Model £887.68 - Standard Practice	NICE guidelines on Social anxiety disorder recognition, assessment and treatment § 6.13.2 Radhakrishnan et al (2013)

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

	Mean discounted cost per patient using the technology (£)	**Mean discounted cost per patient using the comparator (£) The Clark and Wells Model**	**Mean discounted cost per patient using the comparator (£) The Heimberg Model**	**Mean discounted cost per patient using the comparator (£) Standard Practice**	**Difference in mean discounted cost per patient (£): technology vs comparator 1***	**Difference in mean discounted cost per patient (£): technology vs comparator 2***	**Difference in mean discounted cost per patient (£): technology vs comparator 3***
Device cost	£30	£2,788.43	£1863.57	£887.68	-£2758.43	-£1833.57	-£857.68
Training cost	£5	N/A	N/A	N/A	N/A	N/A	N/A
Administration cost	£10	N/A	N/A	N/A	N/A	N/A	N/A
Monitoring costs	£15	N/A	N/A	N/A	N/A	N/A	N/A
Consumables	£10	N/A	N/A	N/A	£40	£40	£40
Adverse events	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total	£70	£2,788.43	£1863.57	£887.68	-£2,788.43	-£1,793.57	-£817.68
	* Negative values indicate a cost saving. Adapt this table as necessary.						

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

N/A

Describe the differences between the base case and each scenario analysis.

N/A

Describe how the scenario analyses were included in the cost analysis.

N/A

Describe the evidence that justifies including any scenario analyses.

N/A

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£)*
Scenario 1 (total costs)	Text	Text	Text
Scenario 2 (total costs)	Text	Text	Text
* Negative values indicate a cost saving. Adapt this table as necessary.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

A Probabilistic Sensitivity Analysis (PSA) used to quantify the level of confidence in the output of the analysis, in relation to uncertainty in the model inputs. In the base case analysis, the point estimate of each input parameter value is used. In the probabilistic analysis, these parameters were represented as distributions around the point estimate. Gamma distribution was used for Costs and Beta for the transition probabilities

In a PSA, a set of input parameter values is drawn by random sampling from each distribution, and the model is 'run' to generate outputs (cost and health outcome), which are stored. This was repeated for 5000 iterations.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Name	User defined	ACTIVE	Deterministic	Probabilistic	Distribution	*Alpha*	*Beta*	*N int*	*N control*
PSA flag		**0**							
Cost of Individual CBT		**£887.68**	£887.68	£842.01	Gamma	£ *887.68*	*1*		
Probability of Response to Individual CBT		**54.20%**	54.20%	57%	Beta	*199.456*	*168.544*	*368*	*679*
Patients per AlphaStim life expectancy		**5.00**	5.00	2.80	Gamma	*5*	*1*		
Per patient cost of Alpha-Stim		**£70.00**	£70.00	£125.04	Calculated				
Probability of Response to Alpha-Stim		**47.20%**	47.20%	40%	Beta	*45*	*55*		

All variables derived from a well-established body of literature and estimations provided by the company.

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

N/A

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

	iCBT		AlphaStim -> iCBT				
	Exp cost	Exp responses	Exp cost	Exp responses	Net Cost	Net responses	Cost saving
MEAN	**1,298,506.65**	**702.21**	**800,361.08**	**884.85**	**-498,145.57**	**182.63**	**1.00**
L95CI	1,201,785.26	651.22	647,302.35	860.67	-652,172.56	140.08	
U95CI	1,398,700.95	753.05	980,042.82	907.58	-320,591.81	226.16	

What were the main findings of each of the sensitivity analyses?

	Expected Cost	Lower 95% CI	Upper 95% CI	Expected Responses	Lower 95% CI	Upper 95% CI
iCBT only	£1,294,233	£1,201,785	£1,398,701	701.68	651.22	753.05
Alpha-Stim	£753,355	£647,302	£980,043	889.24	860.67	907.58
Net	**-£540,878**	**-£652,173**	**-£320,592**	**187.56**	**140.08**	**226.16**

Cost-saving threshold price of Alpha-Stim: £610.88

What are the main sources of uncertainty about the model's conclusions?

Participants were not randomised and there was no control group. Only 48 (29.9%) participants completed every assessment thus control group parameters had to be derived from a limited sample of studies. Another limitation of the study was that the sample lacked ethnic diversity. The sample was drawn from all ages although there were greater proportions of younger and middle-aged participants in the study, reflecting the composition of age groups in routine IAPT NHS services. As expected, the vast majority of patients with GAD were female. There was a broad representation of education, marital status and employment status reflecting the age composition of the sample.

Miscellaneous results

Include any other relevant results here.

N/A

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

Model validation started from the validation of the conceptual design of the model against the current NHS patient pathway. The data that were used were sourced from official NHS reports and well-established published studies. The overall health economics evaluation followed the NICE guidelines for health economic evaluation implementation. Internal quality control of the model was performed by the director of the unit.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

Professor Richard Morriss , Professor of Psychiatry and Community Mental Health at Nottingham University, advised on the response efficiency to Alpha-Stim.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The results of the health economics decision tree model populated with the costs and probabilities for the 8-session standard care model of CBT yielded the results as shown in Table 4. The costs and responses are presented for a cohort of 1000 patients. CES provided a saving of −£540,878 (95% CI [−£648,692, −£327,117]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [141.03, 227.82]). Using the "Clark and Wells model" of iCBT as comparator, CES provided a saving of −£1,637,410 (95% CI −£1,914,463, −£1,175,437]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [141.58, 226.12]). With the Heimberg Model as a comparator, CES provided a saving of −£1,212,463 (95% CI −£1,429,369, −£843,394]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [140.79., 227.71]).

Briefly discuss the relevance of the evidence base to the scope.

The hypothesis tested in the HE model was that adding CES as a second-line treatment in the pathway will eliminate, for the proportion of patients who respond to CES, the need for the more expensive iCBT leading to cost savings.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The hypothesis tested and finally accepted in the HE model was that adding CES as a second-line treatment in the pathway will eliminate, for the proportion of patients who respond to CES, the need for the more expensive iCBT leading to cost savings.
Meta-analysis of previous RCTs of active CES versus sham CES already provides evidence that CES is effective in treating anxiety and depression symptoms which comes in accordance with the response increase shown in the model and its impact on cost minimisation.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

All the data used in the final version of the model referred to resource data for the NHS in England.

The main CBT implementation models were the 'Clark and Wells model' with 14 sessions of 90 min sessions of iCBT, costing £2788.43 in total and the 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT, costing £1863.57 in total.

The CBT session models where derived from NICE guidelines on Social anxiety disorder recognition, assessment and treatment § 6.13.2.

PSSRU 2013 reported costs between £21.98 (computerised CBT) and £141.41 (CBT/IAPT) for the treatment of anxiety and depression. For a more analytic estimation of sessions and cost per sessions time costs were derived for CBT from Radhakrishnan *et al* (2013) for 60 or 90 min of iCBT (£98.59 or £ 176.97 per session) uplifted from 2010 to 2016 prices using the appropriate ratio of 1.09 yielding £ £110.96 and £199.17 respectively.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths-
The health economics analysis followed the NICE guidelines. The PSA provided a reduction in variance of the dataset collected since the data was based on a limited body of literature. All costs were inflated to 2017 values based on the Hospital & community health services (HCHS)Pay & Prices index.
Limitations-
The cost analysis was based on a limited but well-established body of literature due to time and budget constraints of the project. A systematic literature review could potentially uncover more robust costs as well as more relevant comparators for the Alpha-Stim CES intervention. The lack of randomised cohort of great ethnicity mix also affected the effectiveness data as well as the luck of quality of life data forcing a cost-minimisation instead of a cost-effectiveness study.

Detail any further analyses that could be done to improve the reliability of the results.

A randomised clinical trial with the inclusion of quality of data collected via EQ-5D or other tools relevant to psychological interventions that can be translated into QALYs would be desirable.

5 References

Please include all references below using NICE's standard referencing style.

Curtis, L. & Burns, A. (2017) Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. https://doi.org/10.22024/UniKent/01.02/65559

Griffiths, S. and S. Steen (2013). "Improving Access to Psychological Therapies (IAPT) programme: scrutinising IAPT cost estimates to support effective commissioning." The Journal of Psychological Therapies in Primary Care(2): 142-156.

Gyani, A., Shafran, R., Layard, R., Clark, D.M. (2013). Enhancing recovery rates: Lessons from year one of IAPT. Behaviour Research and Therapy 51, 597–606. doi:10.1016/j.brat.2013.06.004

Morriss R, Xydopoulos G, Craven M, et al. (2019) Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder. Journal of Affective Disorders, 253(2019), 426-37.

Radhakrishnan, M., Hammond, G., Jones, P.B., Watson, A., McMillan-Shields, F., Lafortune, L., 2013. Cost of Improving Access to Psychological Therapies (IAPT) programme: An analysis of cost of session, treatment and recovery in selected Primary Care Trusts in the East of England region. Behaviour Research and Therapy 51, 37–45. doi:10.1016/j.brat.2012.10.001

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	March 9, 2020
Date span of search:	January 1, 1981 to March 9, 2020

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Searched Google Scholar, PubMed, PubMed Central

Search terms were “anxiety” “Alpha-Stim,” “CES,” “economics” “cost” “electrotherapy,” “cranial electrotherapy stimulation.” The terms anxiety, electrotherapy, CES, economics, cost, and cranial electrotherapy stimulation were paired with the term “Alpha-Stim” to limit findings to the device in question.

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

www.alpha-stim.com

Inclusion and exclusion criteria:

Exclusion criteria included CES devices that are not Alpha-Stim. Inclusion criteria were studies utilizing Alpha-Stim technology and comparing cost effectiveness of treating with the device.

Data abstraction strategy:

Screened abstracts of returned articles to investigate for inclusion or exclusion criteria. Articles that were not excluded when the abstract was screened were read more carefully for inclusion or exclusion.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text

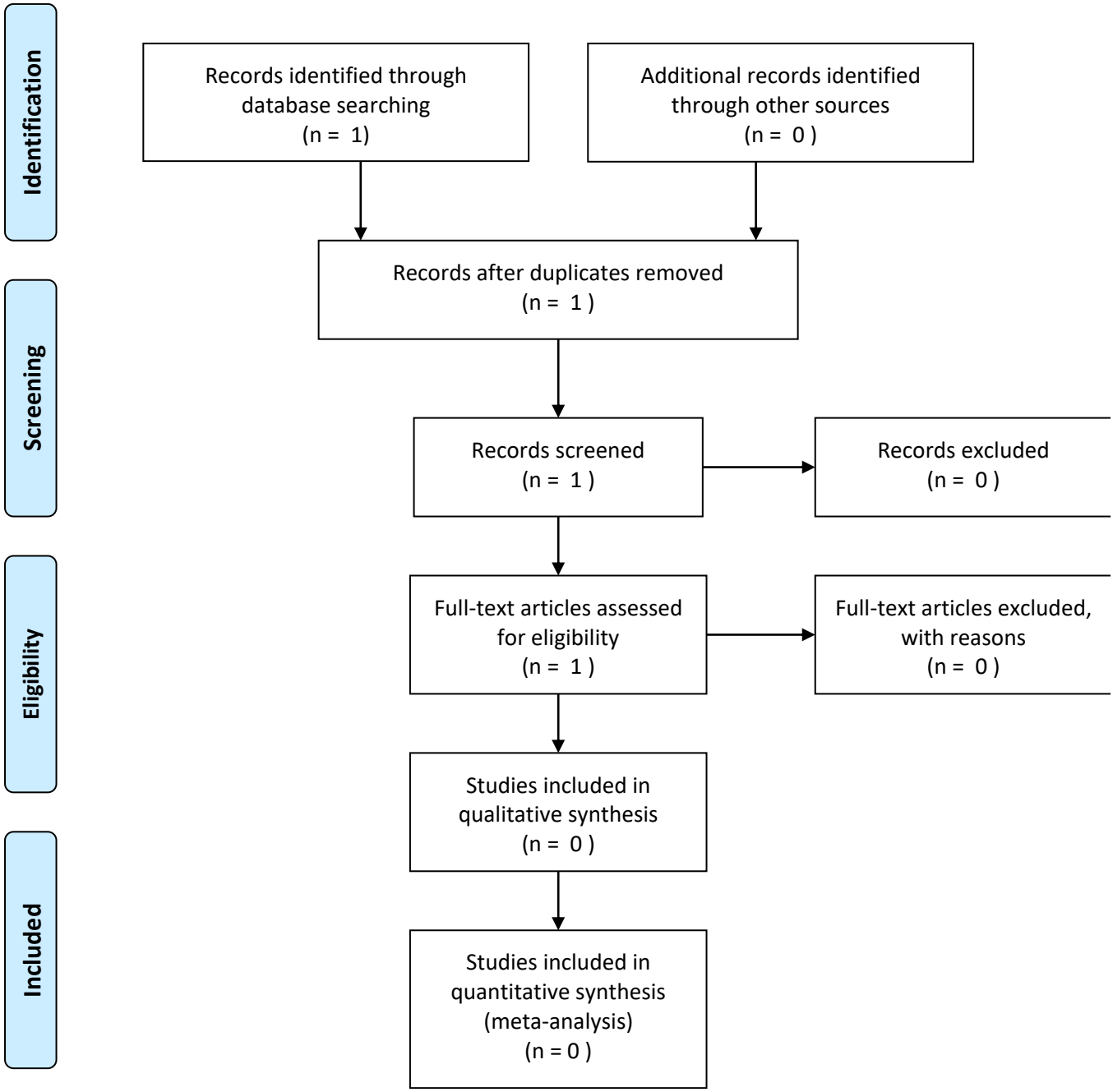
Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

See flow diagram on next page.

Structured abstracts for unpublished studies

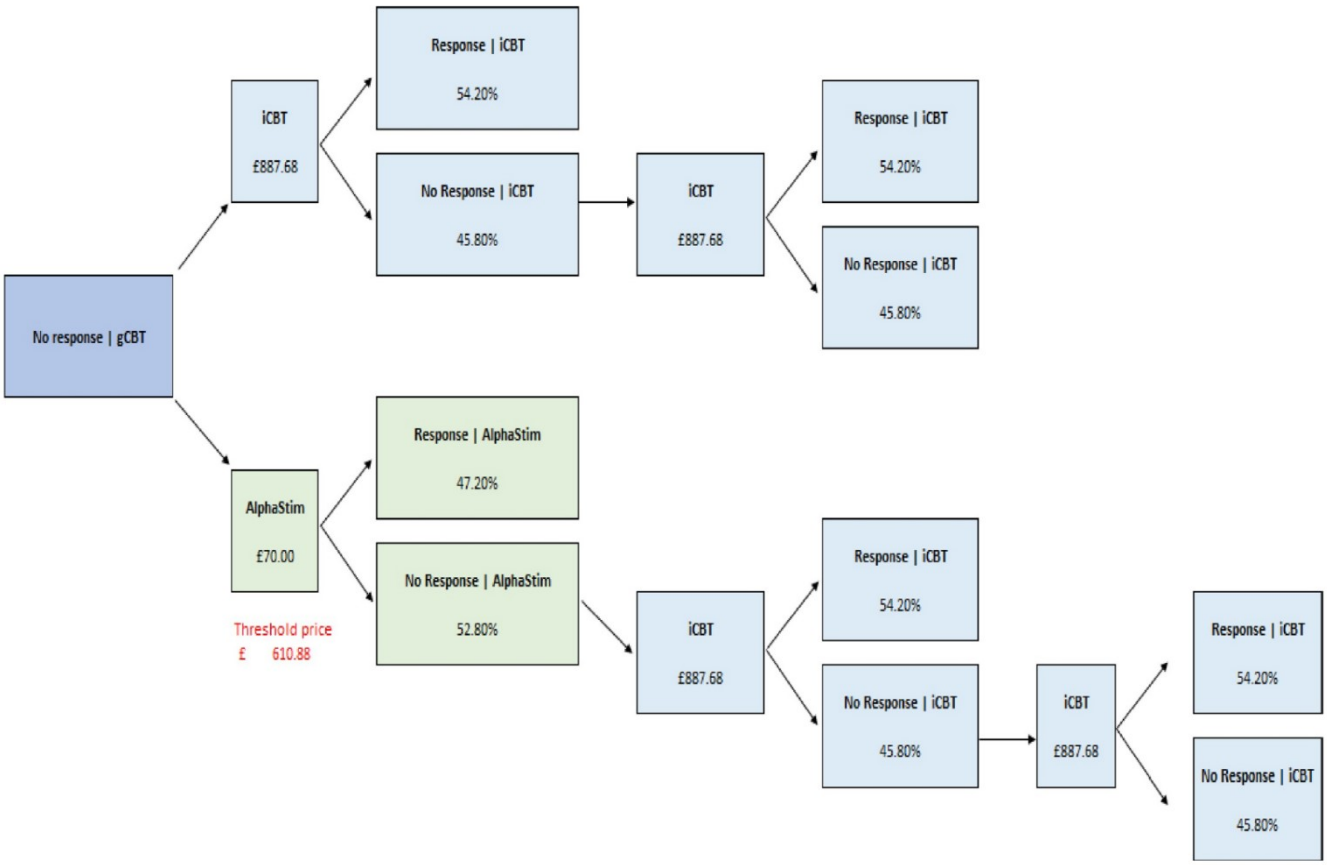
Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

March 9, 2020 Literature search Flow Diagram



Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

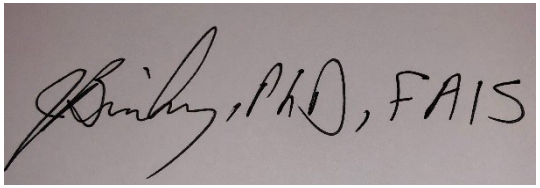
Page #	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	June 11, 2020
Print:	Josh Briley, PhD, FAIS	**Role / organisation:**	Science and Education Director Electromedical Products International, Inc.

Contact email: josh@epii.com

NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: Click here to enter text.

Experts & declarations of interest (DOI)

Expert #1	Dr Chris Griffiths, Senior Research and Evaluation Fellow, Innovation and Research Department Northamptonshire Healthcare NHS Foundation Trust,
	DOI: None
Expert #2	Prof Karina Lovell, Director of research division of nursing, midwifery & social work, school of health science, faculty of biology, Medicine and Health, University of Manchester,
	DOI: None
Expert #3	Prof Cynthia Fu, Honorary Consultant Psychiatrist in the National Affective Disorders Service, South London and Maudsley NHS Foundation Trust; University of East London,
	DOI: None
Expert #4	Prof Richard Morriss, Professor of Psychiatry & Community Mental Health, Faculty of Medicine & Health Sciences, University of Nottingham,
	DOI: Yes

Type of interest *	**Description of interest**	**Relevant dates**	
		Interest arose	**Interest ceased**
Choose an item.	Research funding to University of Nottingham NIHR MindTech Medtech and In Vitro Centre to carry out study of this device in 161 patients with generalised anxiety disorder	**2016**	**2019**

Choose an item.	Research funding to University of Nottingham Applied research Collaboration East Midlands to carry out a randomised controlled trial of this device in primary depression disorder	**2019**	**2022**
Expert #5	Simon Royal, Honorary Assistant Professor Primary Care, University of Nottingham,		
	DOI: N/A		
Expert #6	Dr David Smart, General Practitioner, Leicester Terrace health Care Centre, ,		
	DOI: N/A		
Expert #7	Caroline stevens, CBT (therapist), Notts HC, ,		
	DOI: Click here to enter text.		
Expert #8	James Kustow, Consultant Psychiatrist , Private practice with multidisciplinary clinic on Harley Street (and 1 session of NHS practice in Barnet, Enfield and Haringay Mental Health NHS Trust, ,		
	DOI: I have a dedicated Alpha-stim Clinic in central London, where individuals (who are not under my care) can book in for an Induction Session (charged) and purchase/rent a device. I do not assume any clinical responsibility for these patients, only ensure that they are safely inducted. I also sell/rent devices to my own patients where requested (they are aware that they have the option of buying one on-line and often do). In line with Good Medical Practice, I explain to patients (and document in my Intake/registration form) that as I purchase a number of devices in one go, I attract a discount, some of which I pass onto them (I sell devices £50 less than the RRP), and some of which I retain as an administration fee.		
Expert #9	Roz Shafran, Professor of Translational Psychology , UCL Great Ormond Street Institute of Child Health,		
	DOI I have done some consultation work for Big Health previously which is a digital app and still offer free advice when asked.		
Expert #10	Ifigeneia Mavranezouli, Senior Health Economist, Research Department of Clinical, Educational & Health Psychology University College London		
	Ifigeneia provided advice as a health economist with knowledge of the IAPT services and notes from a meeting with her are included in Appendix 1.		

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office.

Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

For more information about how NICE processes data please see our privacy notice.

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? 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 #1	I designed and manage a post marketing study which sought to provide Alpha-Stim to patients who showed signs of anxiety in Northamptonshire Healthcare NHS Foundation Trust. It is a current on-going project. I am named on an ARC East Midlands funded research project which looks to assess Alpha-Stim in depression in primary care.
Expert #2	Have not used or know about this specific technology
Expert #3	I am familiar with the literature on the Alpha Stim technology, although I have not used it. I have not been involved in the research or development on this technology.
Expert #4	I am familiar with the technology. I have used it in my clinical practice and in research in the past and currently. I have completed a study of the device in 161 patients with moderate to severe generalised anxiety disorder and published it in the Journal of Affective Disorders in 2019. The technology is used in some primary care practices and Improving Access to Psychological treatment Services to treat generalised anxiety disorder. I ask patients to consider purchasing the equipment directly from the company if they are clinically suitable for it and can afford the cost. It is inequitable that people who cannot afford the device are not able to access the device and potentially benefit from it.
Expert #5	I am familiar with the technology having used it in approximately 50 primary care patients. This includes recruits to a small trial I am conducting comparing its use to a usual care model. The trial is coming to a close but several patients continue to use the technology. I have not been involved in the development of the technology and I do not know how widely used it is in the NHS.

Expert #6	I am aware of the research evidence and have had feedback from patients who have used the technology. I have not personally use this. This is being used locally in a study with people with anxiety and COPD in partnership with our local mental health trust with apparently good outcomes without problem
Expert #7	I have used it and am familiar with it in a clinical sense
Expert #8	I first read about Cranial Electrotherapy Stimulation and 'Alpha stim' approximately 5 years ago, but was introduced to it in more detail in February 2018 by a colleague, a respected Traumatologist. We were collaborating as part of the Grenfell Tower Trauma Rehabilitation Programme. (I am the Medical Director of an organisation called The Grove Practice and we have been one of the providers of psychotherapeutic input for the programme). I reviewed the available data and read around the topic, and was provided with a detailed a clinical perspective from my colleague and her team, who had been using it with their clients for a number of years with excellent results in terms of anxiety management, in the context of psychological trauma. We went on to use the technology with a number of patients, as part of the scheme. Over the last two and a half years I personally have used the device for periods, as have a number of friends, family members and colleagues. I've also used it with my private psychiatry patients, but only in the management of anxiety presentations, as my reading of the literature is that it is in this group only where there is sufficiently robust evidence to support its use. I have been very impressed with the results (and tolerability) in generalised anxiety such that it is probably now my 1st line recommendation for this cohort. I have experience using the device with about 150 patients to date, and the majority of them report having benefited from it, in many cases very significantly (to full resolution). I have not been involved in any research or development of the technology. Separate from my clinical practice, where it is one of many treatment modalities offered to patients as indicated, I have established a dedicated Alpha-stim Clinic in central London, where individuals can book in for an Induction Session (which I personally feel is necessary for safe use), and take away a device. There is a rental option, but most patients purchase devices. As far as I am aware this technology is not currently used at all in the NHS (with the exception of the 2019 NHS study).
Expert #9	− Are you familiar with the technology? NO

	– Have you used it? NO – Are you currently using it? NO – Have you been involved in any research or development on this technology? NO – Do you know how widely used this technology is in the NHS? NO

2. Has the technology been superseded or replaced?

Expert #1	No
Expert #2	No
Expert #3	No, there is no other comparable technology at this time with the same level of evidence of effectiveness in the community
Expert #4	No
Expert #5	No
Expert #6	Not my knowledge
Expert #7	I don't think so
Expert #8	Not as far as I am aware
Expert #9	I don't think so – I had never heard of it before

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	It is innovative and novel concept/design for the NHS, although it has been used in health systems in other countries, e.g. USA.
Expert #2	It is a novel concept/design and is very different from current standard of care
Expert #3	The technology is a novel concept in which a low electrical stimulation is proposed to modulate brain activity as measured by EEG (Kennerly, 2004) and functional MRI studies (Feusner et al., 2012).
Expert #4	It is a completely novel concept. Many patients express a preference for non-drug and non-psychological treatment that can be delivered at home. The alternatives are drug treatments, all of which have the potential for addiction or psychological treatments that are not always acceptable toor effective in everyone.
Expert #5	It is certainly innovative in that it offers a non-pharmaceutical, non-IAPT approach to managing anxiety in primary care and as such fulfils an important need and represents a novel concept.
Expert #6	This is a significant advance. There are patients who do not wish for either talking treatments or medication to manage their mood. Also there are many patients who have a physical attribution to their mood and therefore use of a physical device would be more acceptable
Expert #7	Unsure
Expert #8	In my opinion this is a novel concept compared to the current standard of care. There is increasing interest in neuromodulation, particularly with rTMS, but the home use of CES (Alpha stim) in the management of anxiety is a marked deviation from standard practice in the UK.
Expert #9	My expertise is in psychological therapies. The technologies that have been used in anxiety disorders traditionally involve biofeedback.

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	No
Expert #2	No

Expert #3	Alternative comparable technologies which have a similar mode of action potentially include transcranial direct current stimulation (tDCS). Findings to date for tDCS as a treatment for Generalised Anxiety Disorder have been mixed though, which seems to be related to the number of treatment sessions, in which there seems to be greater efficacy with a higher number of treatment sessions (systematic review: Stein et al., 2020). However, there have been a limited number of studies with small sample sizes (systematic review: Stein et al., 2020). Two recent trials which had not been included in the systematic review (Stein et al., 2020) have shown some effects, although the effects were not significant in these pilot studies (Lima et al., 2019, Lin et al., 2019). Lima et al. (2019) randomised sham-controlled trial found an improvement in the physical symptoms of anxiety following 5 treatment sessions, though there were no significant differences in anxiety symptoms between the active and sham treatment arms as measured by the Hamilton Anxiety Scale. Lin et al. (2019) reported an improvement in anxiety symptoms after 10 treatment sessions, but this was not significantly different from the sham controlled treatment arm (abstract: Lin et al., 2019).
Expert #4	Another company Fisher Wallace produces a device delivering cranial electrostimulation but this is worn as a band around the head. I am unsure how similar the waveform is but this company has not conducted trials of their device in patients with primary anxiety disorders to my knowledge so it is unclear how similar or effective their product is.
Expert #5	No
Expert #6	No, I am not
Expert #7	Unsure
Expert #8	There are other companies that produce devices that fall in the Cranial Electrotherapy Stimulation bracket, but it is my understanding that Alpha stim is the product that has been around for the longest and is the market leader. It has also been evaluated in a few reasonable quality clinical studies.
Expert #9	No but technologies is not my area of expertise. It is not routinely used in mental health services such as Improving Access to Psychological Therapies

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	Reduction in symptoms of anxiety and anxiety as measured on the GAD-7. For patients who have chronic illness linked to anxiety (diabetes, COPD, asthma) they could see improvements in these diseases.
Expert #2	Can be completed at home – but there is little clinical or cost effectiveness so much further testing is required – I have only read the abstract as there is a pay wall to access full text – but from the abstract evidence is limited
Expert #3	The technology offers a treatment option for patients who may not want to have pharmacological or psychological treatment as well as for patients who are on a wait list for psychological treatment.
Expert #4	Patients with primary anxiety disorders, particularly those with generalised anxiety disorder, improve in symptoms of anxiety, depression and insomnia, and there are usually associated improvements in work and social function and quality of life as a result. In the study I performed in patients recruited from 2 Improving Access to Psychological treatment services who had not improved with computerised cognitive behaviour therapy, 45% achieved remission of their symptoms of generalised anxiety disorder at 12 weeks and these were sustained at 24 weeks without further CES treatment. The improvements are gradual with 75% of the improvement occurring in the first 4 weeks and further improvements occurring up to 6 weeks with daily use. Patients who would prefer or not responded to other first line treatments for generalised anxiety disorder would improve, whether or not they also have depression or other types of mental or physical disorder. I have used it successfully in patients with bipolar disorder and generalised anxiety disorder in my clinical practice. This technology can be used successfully with psychological and drug treatments for generalised anxiety disorders when these have been only partially successful in controlling symptoms.
Expert #5	A treatment modality that is well tolerated, swift to deploy, and relatively light on health care professional input, not requiring regular review or physical appointments.
Expert #6	Firstly the ease of use with minimal if any side-effects and therefore good safety profile. The fact that it is novel and not using either medication or talking therapies
Expert #7	Reduction of levels of anxiety and depression

Expert #8	Potential benefits to patients - a significant reduction in anxiety symptoms without the need for potentially harmful medication, or the need for psychological input.
Expert #9	Easy; no need to engage in a talking therapy if that doesn't appeal. It can help treat the unmet need as you don't need a qualified clinician to administer it. Relatively short period of time before impacts are made.

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	People who not wish to use medication, people who are on multiple medications and there could be anxiety medication interactions, people who are house bound or do not have access to independent transport to travel to medical appointments, people who do not wish to have psychotherapy, people who do not respond to anxiety medication, people who do not respond to CBT for anxiety, young people
Expert #2	As above
Expert #3	Patients who do not wish to have pharmacological or psychological treatment.
Expert #4	People with severe generalised anxiety disorder who also have moderate depression symptoms as well seemed to particularly benefit in the study that I conducted. Those with improvements in these depression symptoms seemed to show sustained improvements beyond 12 weeks to 24 weeks without further treatment. They also showed a greater overall rate of remission.
Expert #5	Young working people who don't want to take medication and/or haven't the time to engage in IAPT.
Expert #6	I think in particular people with common mood disorder and especially those with long-term conditions he may have problems with side-effects mother medication is would be of particular help
Expert #7	People with GAD and mild to moderate depression, possibly recurrent depression, chronic depression. People trying to reduce pain medication, sufferers of long term conditions, mild to severe demotivation.
Expert #8	Although many people can benefit from using CES, in my opinion it will be particularly useful for individuals who are reluctant/unable to take psychotropic medications (for whatever reason) and for those who are unable to engage with psychotherapy. Its use may be even more impactful and appropriate in a post-Covid world for various reasons.

Expert #9	Those that do not engage in brief psychological interventions and who would prefer not to take medication

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	Yes, it could fit into stepped care for anxiety in IAPT, offered through GPs, mental health and community services. If research showing improvements are replicated in NHS service application (and Morriss et al. 2019 indicates this) then it could lead to improved outcomes (anxiety and related diseases), fewer hospital visits or less invasive treatment (i.e. avoiding need for medication or psychotherapy)
Expert #2	Possibly but requires a robust evaluation
Expert #3	For some patients, this technology could lead to fewer visits.
Expert #4	Yes. In the study that I conducted, 50 per cent of patients who were waiting for individual cognitive behaviour therapy did not wish to receive it because they had already improved. It would increase the capacity of Improving access to psychological Therapy services to manage a greater throughput of patients, particularly those who did not improve with low intensity psychological treatment. It is loaned at a similar price to drug treatments for generalised anxiety disorder, replacing the need to prescribe them and reducing the cost to the NHS of drug dependence from benzodiazepines. It is much cheaper than drugs such as pregabalin and course of individual cognitive behaviour therapy (by £550 per person). .The device is well tolerated in people with physical illness so it would help treat patients with anxiety disorders or mixed anxiety and depression with other physical health problems who might not be able to access psychological treatments or drug treatments that are poorly tolerated. I have seen ths treatment work well in patients with multiple sclerosis as an example. It would also decrease anxiety and reduce unnecessary use of health services because they become excessively anxious about their health or phobic of procedures such as surgery that they require.
Expert #5	It may lead to improved outcomes for the patients but it certainly necessitates fewer visits nad reduces long term prescribing.
Expert #6	I think there is definite opportunity for this to be used within long-term condition pathways reducing hospital admissions where we know that improvement in mood disorder could reduce emissions by up to 28%

Expert #7	I believe so
Expert #8	Undoubtedly this technology has the potential to reduce the burden on mental health services directly, primarily by reducing the number of individuals referred for psychological treatment. If all patients with generalised anxiety disorder were provided with a device, in my experience, a large percentage of them would improve without the need for more costly and time-consuming interventions. If used efficiently, I believe there would be a reduced cost burden compared with the current model.
Expert #9	From what I have read (which is limited), yes, I believe it would.

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	Lower costs due to avoiding treatment which is more expensive (face to face psychotherapy)
Expert #2	Blank
Expert #3	Potential benefits include offering another treatment option for patients who might prefer this treatment and improving outcomes by offering an immediate treatment while being on a wait list for psychological treatment.
Expert #4	Greater choice so more patients with anxiety disorders will accept and receive effective treatment in primary care and general hospital settings. Greater throughput and effectiveness of services such as Improving Access to Psychological Treatment Cost savings with more efficient use of resources. Improvements in recovery in patients with serious mental illness so can return to work, get off benefits and stay well without elapse.
Expert #5	More patient empowerment, fewer physical visits, less prescribing
Expert #6	Improved access to treatment for people with mood disorder, reduction in symptoms and therefore reduced use of primary and secondary care services. For some people dealing with particular trauma they may be help and returning to the workplace in people with anxiety
Expert #7	Greater stability for this group of patients, less medication, less clinic visits, reduced therapy time

Expert #8	In addition to the potential cost savings described above, the central benefit of Alpha-stim would be an overall improvement in mental health (as a result of its effect on anxiety which is extremely prevalent and not particularly well managed presently). There are likely to be significant secondary benefits (in terms of work productivity etc)
Expert #9	Most people with mental health disorders do not get treated. When they do get treated, the quality of that treatment is highly variables. Outcomes are variable and there is definitely room for improvement.

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	There would be initial costs in setting up and buying devices, following this there could be a reduction in anxiety and related disorder treatment costs
Expert #2	Possibly more each device costs £450 and understand that it can be shared but assuming that can only be used by one individual at a time
Expert #3	Blank
Expert #4	It is likely to be cost saving per patient and allow a greater throughput of successfully treated patients for the same cost to the health care system. More patients with generalised anxiety disorder are likely to be treated successfully as more patients will accept treatment overall because they would prefer it to drugs and psychological treatment.
Expert #5	It depends on the cost of the units and the practicalities of re-using these. I would say at worse the cost is likely to be about the same as current standard management, probably less.
Expert #6	Technology when used and especially if could have repeated the patient uses is likely to be highly cost-effective especially compared to treatment as usual for psychological therapy services
Expert #7	Unsure
Expert #8	There will obviously need to be an upfront investment, as devices will need to be purchased or rented for use with patients. I think that if the technology is used efficiently and sensibly, there are likely to be significant cost savings down the line as a consequence.

Expert #9	I don't know but if I understand correctly from the trial, patients self-adminster the intervention so it should be very low cost.

10. What do you consider to be the resource impact from adopting this technology? 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?

Expert #1	Initial required resources to buy and introduce the devices. Device simple to use and show patients how to use, so no change in staff required.
Expert #2	Without a clear economic analysis then this is difficult – i.e. the cost of the device he company states typical usage based on an individual patient treatment of 10 weeks use (including additional staff time, postage and consumables cost, estimated at £40), per patient treatment cost is £70 and there is the training – so it is likely that it may well be less effective as stated in their paper and potentially more expensive than current provision
Expert #3	The technology might shift the care setting to primary care for some patients.
Expert #4	More patients are likely to be treated in primary care and community care settings with a shift from secondary care and Improving Access to Psychological Treatment services (they will be treated before receiving high intensity psychological treatment). Can be shown in 5-10 minutes so does not have extra staff or equipment implications.
Expert #5	Changing the structure of primary care mental health pathways to make them more nurse-led with less emphasis on prescribing and regular review visits.
Expert #6	Reduction in use of psychological therapy services reduction in attendance at primary care and hospital services opportunity for mood disorder to be managed within social prescribing services and therefore opportunity for increased involvement of voluntary sector engagement in mood disorder
Expert #7	I think there could be more focus on a large cohort of patients being maintained in a more remote way.
Expert #8	I think the resource impact from adopting this technology would include reducing the number of face-to-face psychotherapy sessions required, allowing staff to be redeployed in other areas. If used in emergency settings (to reduce arousal/distress/aggression), it could possibly impact the number of violent assaults on staff. I think there is a role for technology in primary care, mental health

	secondary/tertiary care and in emergency settings. There may also be a role in dental health care where it is common for anxiety to present and impact effective delivery of care.
Expert #9	change the number or type of staff needed – yes, both since it is self-administered change the need for psychological treatment or medication change the setting from clinic to home empower patients

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	Yes staff need to know to use the device, but this only takes 10 minutes to learn
Expert #2	Yes they state that staff need to be trained
Expert #3	Staff would require initial training to use the technology.
Expert #4	Staff in primary care need to be shown how to use the equipment but can be easily trained through a video and telephone support from the distributors.
Expert #5	Minimal
Expert #6	Minimal amount of training
Expert #7	Ideally a therapist, step 2 or 3 IAPT, but would need training regarding the device. Could fit well within existing IAPT structures
Expert #8	Staff would need to be trained how to induct people to use Alpha-stim. This could be done in a single training session (1-3 hours). Devices would need to be purchased and periodically checked / serviced (usually only a change of batteries (Lithium) is required).
Expert #9	The clinician would need to set the device appropriately

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	No
Expert #2	No but it is not clear that any safety tests have been conducted though they suggest it may be okay in pregnancy and children need to be supervised – why is this ?
Expert #3	I'm not aware of any safety concerns.
Expert #4	It has an excellent safety record. Only 4 out of 161 patients stopped using the device because of side-effects and there are no reported deaths or serious incidents attributed to this device. It has CE and FDA regulatory approval for sale direct to the public across Europe and United States.
Expert #5	No
Expert #6	No particular concerns
Expert #7	None that I am aware of
Expert #8	Alpha stim may affect the operation of cardiac pacemakers (particularly the demand type pacemakers) so it should not be used in this patient group. Safety has not been established for use in pregnancy therefore this should be a contraindication. When using Alpha-stim AID, the ear clips should not be used on any other body part other than the earlobes. Generally adverse effects are very rare when used correctly In the US, Alpha-stim is only available on prescription (when guided by a Healthcare professional). Personally, I think this is advisable in the UK, as getting the current level/time optimised can be tricky/confusing, and there are potential risks. It is also important that the technology is used properly and safely.
Expert #9	No but this is the part that concerned me most. All that was said in the trial was that participants experienced no adverse effects but there was insufficient information on this. If patients are told that they have a 'brain' problem that this device can help with, where does that leave them with regard to engaging in a psychological treatment. What are the long-term effects of the intervention? Those were the two main concerns/comments that I had.

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	Need buy-in from clinicians to introduce. This takes time and is best delivered via face to face engagement. There are practical issues: device needs to be used correctly and supplies of spare connectivity fluid, ear pads, lithium batteries (widely available), need to wiped clean with disinfectant prior to handing to another patient
Expert #2	Only apps
Expert #3	I am the Chief Investigator of a Rosetrees Trust funded clinical trial on transcranial direct current stimulation (tDCS) as a potential treatment for major depression in the community, and we have been investigating transcranial alternating current stimulation (tACS) as a potential treatment for mild symptoms of depression. I am the senior author of a meta-analysis of the efficacy of non-invasive neurostimulation treatments in depression (Mutz et al., 2018) and co-author of a meta-analysis of the comparative efficacy of non-invasive neurostimulation treatments in depression (Mutz et al., 2019). I have published research on the neuropsychological effects of tDCS (Edgcumbe et al., 2019).
Expert #4	This is a safe and easy to use device. Drug treatment for generalised anxiety disorder is with antidepressants, addictive or expensive drugs. Psychological treatment services cannot meet the demand for this condition which affects 4% of the population. It costs £500 per device to buy privately so at the moment people on low incomes are discriminated against by not being able to afford the device. I see this therefore as a problem of inequalities affecting poorer and minority groups.
Expert #5	Nil
Expert #6	We are just about to start a study using this with our primary care liaison worker workforce
Expert #7	I noted that patients with difficulties of emotional regulation did not do so well with the device. Emotionally unstable personality traits were I felt a contraindication to use of the device. People who were still in later stages of grief or loss found their emotions uncomfortably heightened.

Expert #8	Some individuals are exquisitely sensitive and will experience vertigo at very low doses. In this group it is sensible to 'start low and go slow' (i.e. allow the individual to adjust to very low current levels for a period, before increasing cautiously). Be cautious in individuals who are prone to vertigo, nausea or dissociation.
Expert #9	It is an appealing technology but the work that has been done to date is preliminary and needs replicating by an independent research group before it can be rolled out by the NHS. There has been no RCT comparing its effect to psychological treatment including low-intensity interventions for anxiety.

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	GAD prevalence in the general population is around 4 to 7%.
Expert #2	Not sure as we know as unclear what uptake was from the abstract of the Morriss 2019 paper
Expert #3	Blank
Expert #4	In my study, one in seven people offered the opportunity of having this device with severe generalised anxiety disorder, took up the offer when a course of treatment was offered free of charge. Given that required participation in research then the uptake might be higher than this. In any given 12-month period 4 per cent of the population have generalised anxiety disorder and 1.3% seek treatment from the NHS. I estimate the device might be used by 1 in 6 or 1 in 7 of these help seeking patients assuming all were offered it as a choice. On top of this, some additional patients will seek treatment with this device who would not otherwise seek treatment given the demand after I published my study.
Expert #5	I think anyone with minor anxiety or depression would be eligible for this – that's a lot of people!
Expert #6	Significant number of people as common mood disorder. Has high incidence in the population. However I think particular targeted approach and long-term conditions would be highly cost-effective

Expert #7	Unknown. However I would imagine that all patients in Honos clusters 1-4 could potentially benefit, and these patients are very likely to be referred to IAPT services.
Expert #8	I wouldn't be able to provide specific numbers, but a large proportion of individuals presenting to primary or secondary care with Generalised Anxiety Disorder. It may also have a role in other anxiety disorders (e.g. social anxiety disorder or anxiety symptoms associated with Post Traumatic Stress Disorder) but this probably requires additional evaluation in clinical trials.
Expert #9	The trial that has been conducted had several important exclusion criteria in terms of medication stability, other diagnoses as the primary problem etc. I don't know the answer to this question but I would say that it is broadly applicable to those with generalised anxiety disorder according to the research.

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	Both
Expert #2	Probably an addition
Expert #3	Both, the technology could be a potential first line treatment as well an add on for current treatments.
Expert #4	It would sometimes replace and sometimes add to current care.
Expert #5	Addition to current standard care
Expert #6	This could be used with other treatments therefore is an addition or replacement
Expert #7	Could replace some step 2 and 3 face to face therapies, or work as an adjunct to step 2 groups. I think some step 2 and 3 clients could do without therapy completely and some could get by with occasional 'check in' face to face appointments, and some could have phone contact only.
Expert #8	In some cases it could replace current practice, and in other situations serve to complement the current standard of care.

Expert #9	There are insufficient research data to answer this question.

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	There are practical issues: device needs to be used correctly and supplies of spare connectivity fluid, ear pads, lithium batteries (widely available), need to wiped clean with disinfectant prior to handing to another patient. Getting the device back from the patient.
Expert #2	Don't know
Expert #3	The technology is usable and generally well tolerated.
Expert #4	No it is easy to use. Takes 5-10 minutes to show how to use. Staff should telephone within 72 hours of use of the machine to see if there are any questions that the person might have about using the device. Sometimes patients need changes of duration of treatment or the setting.
Expert #5	Not particularly.
Expert #6	It can cause some irritation around the ears where the electrodes are applied however it is easily used
Expert #7	I noted that some asylum seekers or victims of torture did not find the technological aspect appealing, or that it used electricity.
Expert #8	– I feel an induction session with someone trained in the use of Alpha Stim is required for safe and effective use. There is often confusion around what level of current to use and for how long i.e. dosing. It is also important to screen for the presence of cardiac pacemakers the primary contraindication, and discuss the lack of data in pregnancy in women of childbearing age.
Expert #9	I don't know

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	Funding.

	Needing a process for identifying and offering to patients with anxiety Agreement from national IAPT to introduce to local IAPT provision.
Expert #2	No
Expert #3	No
Expert #4	None. Main reasons for non-adoption are that NICE have not approved it or they have never heard of the treatment.
Expert #5	Cost of units
Expert #6	The lack of attention that common mood disorder has within the NHS. Despite its high prevalence major cause of suicide. It is a surprise that more attention has not given to it. Previously there has been little workforce that could address this however now we have social prescriber link workers. There is a major opportunity for this to be utilised and then delivered through a national workforce program
Expert #7	Non return of Alpha stims, but this was a very small minority of patients, particularly in student populations. All asylum seeker patients returned their devices once they had used them. .
Expert #8	No
Expert #9	I think the question of harms is critical. Psychologists treating anxiety (including me) won't and don't understand the mechanism by which this device is meant to be effective at alleviating anxiety so the lack of understanding of mechanism of action may also be a barrier. There is also a need for longer term outcomes

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	No
Expert #2	No
Expert #3	No

Expert #4	Veteran's Administration systematic review and meta-analysis (P Shekelle et al Annals of Internal Medicine 2018). Unpublished secondary analysis of depression and anxiety in my previous study (currently under review by a journal).
Expert #5	No
Expert #6	I'm aware that there is a study which we are also taking part in concerning management of depression in general practice using this technology with Prof Morris of Nottingham
Expert #7	Unknown
Expert #8	I have not received a list of evidence to date, as far as I am aware
Expert #9	No

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 within the NICE process and will not be shared or published.

Expert #1	ARC East Midlands funded research project which looks to assess Alpha-Stim in depression in primary care. A post marketing evaluation study that I am undertaking (this is not research) – yes willing to share results, will have results by end 2020/early 2021
Expert #2	No
Expert #3	No, I'm not aware of locally collected data on this technology.
Expert #4	Audits of data are going at some primary care sites but I do not have access to this data.
Expert #5	I am working on an economic analysis to accompany my service evaluation. I would be happy to share this with NICE.
Expert #6	I'm aware that there is a study which we are also taking part in concerning management of depression in general practice using this technology with Prof Morris of Nottingham

	It is not my gift to be able to share however, Prof Morris should be approached directly
Expert #7	Unknown
Expert #8	No I am not involved in research. I am a clinician.
Expert #9	No

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	A sufficiently powered multi-site RCTs (one for adults and one for children and young people) with primary outcome of anxiety in the UK would add to existing evidence base.
Expert #2	Yes – from what I could ascertain from the abstract as cant access full text – requires a full trial showing clinical and cost effectiveness and acceptability
Expert #3	The sample size of the RCT of the technology in Generalised Anxiety Disorder was small (n = 115) (Barclay and Barclay, 2012). In the patient cohort study, there was a low take up for the study as 22% of potentially eligible participants agreed to take part and there was a discontinuation rate of 30% by week 6 (Morriss et al., 2019). The mechanisms of the technology in generalised anxiety disorder are not well understood as studies which had measured EEG (Kennerly et al., 2004) and functional MRI (Feusner et al., 2012) were in healthy participants. Long term outcomes and prevention of relapse have not been investigated.
Expert #4	I am about to start a sham controlled randomised controlled trial, delayed by Covid-19, of alpha-stim cranial electrostimulation in patients with primary depressive disorders of moderate severity with or without anxiety disorders in primary care. This trial may help to determine if there is specificity of the effects of this technology in anxiety disorders or if the device is effective in both anxiety and depression disorders. Would be desirable to apply the latest MEG and fMRI technology to test claims about the mechanism of action of a course of CES in people with generalised anxiety disorder. I do not know of anyone who has been funded to carry out such a study.

Expert #5	This needs a large scale RCT.
Expert #6	Longer term patient feedback word I think be helpful to bolster the evidence and also support implementation and overcome any patient barriers
Expert #7	Unknown
Expert #8	I think good quality studies looking at its use in PTSD and other anxiety disorders would be a useful next step. Further studies in GAD would also be helpful, as data is still limited.
Expert #9	I think more work needs to be done on potential adverse events; it is essential to establish whether the technology is more effective than existing psychological treatments and its longer term impact.

Appendix 1

MT477 Alpha-Stim for anxiety disorders
Meeting with Health Economist with knowledge of IAPT service – 19/08/202
Notes prepared by Cedar EAC.

Key Areas for Committee Consideration
The EAC and NICE had a meeting with a health economist with specialist knowledge of the IAPT pathway to discuss the economic model inputs presented in the EAC Assessment Report.

A number of areas for committee discussion and consideration were highlighted during the meeting.

Quality of the data used in the model
As stated in the EAC assessment report, there are no RCT studies from which to draw any comparison data (Alpha-stim versus standard care or alpha stim followed by individual CBT (iCBT) versus iCBT alone) to use in the economic model. The EAC has taken steps to validate the data used in the model with the clinical experts however the EAC acknowledges that there will still be concerns with the quality of the data. In particular, the response rates used in the model should be given careful consideration and discussion (see notes on response rates below).

Model decision tree
Neither the company model decision tree nor the EAC model decision tree may accurately reflect the complexities and variability within the clinical pathway for patients however the EAC decision tree modifies the published model by Morriss et al. (2019) and in addition attempts to account for medication use as a treatment option. The EAC decision tree model is therefore considered likely to be the one which most closely reflects the current clinical pathway.

Committee discussion should give consideration to the fact that medication will, in some cases, be used alongside alternatives such as iCBT and Alpha-Stim. The EAC has no basis to assume that medication would be used differentially across the two treatment strategies. It should be noted that the EAC base case, although including a proportion of patients taking medication, does not include any response rates to medication.

Alpha-Stim Uptake
Although the EAC model attempts to account for the fact that only 22% of patients agreed to use Alpha-Stim (Morris et al 2019) in the model, discussion with experts suggests that the uptake rates

may not be relevant to this model as patients who do not start Alpha-Stim do not incur the cost of Alpha-Stim treatment and therefore do not affect its cost-effectiveness.

What should be considered is the impact of patients who start Alpha-Stim treatment but do not complete it. The EAC acknowledges that there are a number of patients who do not complete their treatment (see page 83 of EAC Assessment Report) suggesting that non-completion of treatment in this population may be a concern.

This is supported by results from Morris et al (2019) which reports that 24.2% (n=39) of patients stopped Alpha-Stim treatment by week 6 and 30.4% (n=49) stopped Alpha-Stim treatment by week 12.

Response Rates

The EAC base case is based on the assumption that the probability of a response to Alpha-Stim is 0.47 and the probability of response to iCBT is 0.54 however discussion with an IAPT expert has suggested that careful consideration should be given to the response rates used in the model. It should be considered that some patients who do not respond to Alpha-Stim, may not respond to iCBT either (i.e. refractory to treatments of any kind), and the probability of response to subsequent iCBT might be lower than 0.54.

The EAC acknowledge that there is a possibility that response rates for patients may not be consistent through treatment. Response rates may be impacted by a number of factors including whether a patient completed their treatment or whether a patient had any additional treatments in combination with alpha-stim. For example, results from Morris et al (2019) also reported that by week six, 29.2% of patients had received iCBT and by week 12 49.7% (n=80) patients had received iCBT. The model published by Morriss et al. (2019) does not include medication, which may be in widespread use in clinical practice.

The company model and the EAC model currently include response rates based on published literature which have been validated by clinical experts however this means that given a cohort of 1,000 patients, the cumulative response rate for Alpha-Stim followed by iCBT is 73.6% in the company model and 58.2% in EAC model. While this may be plausible, data from Morriss et al suggests that the 47% response to Alpha-Stim may be confounded by the fact that some patients had iCBT and that the response rate when considering patients who only had Alpha-Stim and patients who had Alpha-Stim plus iCBT, the response rates might be very different. In Morriss et al (2019) using data from table 3 suggests that the response rate at 24 week follow up was 47.8% for all patients, 65.4% for patients using Alpha-Stim only and 30% for patients with both Alpha-Stim and iCBT (based on calculations made using data from table 3 of the publication).

It should be noted however that the text of the Morriss publication suggests that the response rates for patients receiving both Alpha-Stim and iCBT are much higher at 68%.

Some possible points to consider include:

- Were these patients hard to treat anyway?
- Why did they receive iCBT in the first place? Was it because they did not respond in the first two weeks?
- Did they want to stop alpha-stim?
- Did they deteriorated or did they have heavier symptoms from the start and were selected to have combined treatment?

Costs used in the model

Costs for alpha-stim have been provided by the company and therefore are considered to be accurate.

The costs of iCBT were sourced from literature and the costs have been validated by the EAC with clinical experts. Discussion with the IATP expert suggests that some consideration should be given to the components used to derive the single iCBT session cost and it may be more appropriate to use PSSRU costs (hourly rate for a Psychologist). It was discussed that there are problems with using this approach too in that the PSSRU costs may not be entirely reflective of all costs associated with iCBT delivery.

The 2019 PSSRU includes Clinical Psychologist hourly rate of £54 based on Band 7 salary plus overheads (page 111 and page 113). On this basis a 60 minute psychologist iCBT session may be costed at £54 and a 90 minute session at £81, both of which are lower than the costs than those used in the current model. It should be noted that the hourly rate includes indirect costs too, i.e. time spent reviewing patient notes, planning, and meeting with supervisors and do not report qualification costs for clinical psychologists. Discussion with the expert has indicated that a possible alternative would be to use costs from an alternative publication:

Mavranezouli et al (2020) Cost-effectiveness of psychological treatments for post-traumatic stress disorder in adults

The 2019 PSSRU also provides a unit cost for “IAPT adult and elderly” of £96 (page 36), citing the National Schedule of NHS costs as its source, but with no further information on what the cost

represents. Expert advice suggests that these costs may include band 6 or even band 5 therapists that provide low intensity interventions

The National Schedule of NHS costs includes the HRG code MHCC02 Cluster 02: Common mental health problems (low severity with greater need) with a unit cost of £317 per case, based on observed service activity submitted by community mental health services.

Cost Savings

Currently the results of the model suggest that Alpha-Stim is the dominant treatment even when uptake and response rates are very low. While this may be the case, discussion with an expert has suggested that this dominant effect is likely the result of the response rates used in the model. There is a concern that the response rates used for iCBT after a failed course of Alpha-Stim is too high, and that actually patients who fail Alpha-Stim are likely to have a much lower response rate to any subsequent treatment.

Given the concerns with the response rates highlighted in the previous point, the cost savings should be considered with some caution.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT477 Alpha-Stim AID for anxiety

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs 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 captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	20/05/2020	**Company** Initial questions	Could the company provide some insight as to why the variation to the population? • Should Alpha-Stim not be used by patients with diagnosed anxiety disorders? • Is this variation to do with the available evidence or is the company suggesting that people with diagnosed anxiety disorders would limit the use of Alpha-Stim? Could the company clarify the age demographic that the device is suitable for i.e. children and adults?	Stated that mental health on spectrum and that patients do not need to meet full diagnostic criteria for GAD to benefit from Alpha-Stim. For instance, some people with confirmed primary diagnosis of other mental health conditions may not be diagnosed for anxiety disorders. Prof. Morris suggested broader scope to include patients with symptoms of anxiety but without a diagnosis of an anxiety disorder. Alpha-Stim can be used for children as well as adults.

2.	20/05/2020	**Company** Initial questions	What version of the device is currently available/would be provided to the NHS? It will be helpful to note what changes made to the device although mode of action has not changed.	AID version is currently available. Alpha-Stim M can also treat pain. Core device and mode of action unchanged between different versions of the device. The evidence from the older versions of the device is applicable to the current version. The latest model (AID) has been significantly modified, with new electronic features to help usability. The device has an option to lock the treatment cycle which can be very useful for clinicians and an alert feature to tell the patient when the device isn't connected. Over time the device has dramatically reduced in size and external appearance and functionality with no change in mode of action.
3.	20/05/2020	**Company** Initial questions	Additional question depending on response above: • Could the company comment on the fact that different versions are available to purchase online? • How does the company regulate the resale of older models?	No other versions available to buy but company aware that a small number of second-hand versions come up for sale on Ebay etc. The UK distributor does not have any control on resale. The UK Distributor offers no support for these devices.
4.	20/05/2020	**Company** Initial questions	The electrical pulse generator is operated by 2 1.5-volt batteries, How long would batteries last in typical use, FAQ suggest 20-30 hours. How long is typical use for anxiety? Web page suggests for depression 20mins -60mins every day to start any plans for rechargeable version	The device uses lithium batteries which last about 40 hours or 1 month use (£2.50 in battery costs). Company will supply batteries. Average use 20- 60mins/day. Increase intensity to start, reduce setting until no more dizziness (sub-perception). At a setting of <2 (level 1)= 1 hour use >2.5-3 = 20 mins. Can lock device at level 1

				Not demonstrated that patients develop tolerance to treatment. Rechargeable version not currently available but likely in future (both AID and M).
5.	20/05/2020	**Company** Initial questions	Point of clarification There is a suggestion that patients may need more than one device. “participants were able to utilize the same Alpha-Stim device repeatedly during each study.” • Could the company clarify this point? Is there an expectation that patients may need to replace devices? • Could the company comment on the patient specific, non-reusable parts of the device? • Could the company comment on whether the device is recyclable? • Does this depend on recycling facilities available? Does the user have to break up the device in any way to dispose of it sustainably?	No service requirement. Current model – if not working it switches of and will sound an alarm also if clips not applied properly. No experience for needing to recycle the device. If it is broken, send it back to the company to be fixed.
6.	20/05/2020	**Company** Initial questions	Could the company provide some insight as to why the meta-analysis is highlighted ‘Academic in Confidence’ Royal 2020? All studies included in the meta-analysis appear to be published and publically available therefore it is unlikely that all of this information could be classed as confidential. If any of the data in the individual studies is confidential (for example, updated results from trials that have not yet been published), this should be highlighted both in section 6 and in section 7. The company should be aware that the EAC may undertake their own meta-analysis of the published data and if the data are all publically available, the results of the EAC analysis will not be considered to be confidential.	NICE: There is a plan to publish the results therefore company and NICE will look at AIC section again. Happy to work with company on this. EAC can do meta-analysis of their own with the published data.

			Please could the company consider which specific aspects of the meta-analysis should be considered academic in confidence?	
7.	20/05/2020	**Company** Initial questions	Price 2013 listed in table 2 of submission, link doesn't work Please supply a copy	Document sent by company
8.	20/05/2020	**Company** Initial questions	Do patients use medication as well as Alpha-Stim?	Both can be used during therapy as is shown in the Paroxetine study. Initially it was an alternative to medication – there are lots of people who buy the device directly because they want to come off medication. We would like to see people using the device as a first line treatment before medication as a treatment for anxiety, along with drugs for depression.
9.	20/05/2020	**Company** Initial questions	How long does device last for?	If you're going to get an improvement you'll see it in the first 8 weeks. After that the device is returned to the NHS provider. Can treat 20-25 patients in a year with one device.
10.	22/06/2020	**Company** Follow-up questions	Part of the clinical pathways in Section 3 of the evidence submission describe "Telephone support within 72 hours". Can the company clarify who would provide this support?	This would be provided by a practice nurse.

11.	22/06/2020	**Company** Follow-up questions	The company's proposed pathway indicates, but doesn't explicitly state, that at the end of 6 weeks of Alpha-Stim treatment the following options are available: • Stop Alpha-Stim treatment and return device if GAD-7 score shows ?? remission • Re-enter pathway at the same point to consider drug treatment of high intensity psychological interventions if GAD-7 score ≥10 • 6 weeks more Alpha-Stim treatment if patient shows partial response, e.g. 25-50% reduction in GAD-7 score and ≥8 Please indicate if these options are correct. And what GAD-7 score would indicate the treatment can be stopped?	We would suggest a maximum of 8 weeks treatment initially rather than 6. Stop the Alpha-Stim treatment when the GAD-7 score reaches 7 or below - this is remission as measured by IAPT services. Remission may be achieved happen before the 8 weeks treatment is completed so the patient has the option of returning the device at this point. The second option applies after 8 weeks, if the third option of a 5 point GAD-7 reduction hasn't been achieved We would recommend a further course of Alpha-Stim treatment, up to 8 weeks, if the patient has achieved a clinically significant reduction of 5 points or more on the GAD-7 scale during the first 8 weeks. I have attached a document with a revised flow-chart for pages 12 and 13 that I hope clarifies the situation and answers your questions below. **Files included in Appendix 1.**
12.	29/06/20	**Company** Follow-up questions	In each of the 3 settings in your submission (page 12-13) can you check over the following information: • Criteria for starting Alpha-Stim (GAD-7 score) • Duration of initial Alpha-Stim treatment • Criteria for stopping Alpha-Stim treatment • Criteria for extending Alpha-Stim treatment • Duration of extended Alpha-Stim treatment	Please attached the revised flow-chart. GAD-7 of 8 or above is the criteria to start CES 6 weeks initial treatment GAD-7 7 or below patient stops the treatment. GAD-7 8 or above after 6 weeks patient is offered further 6 weeks Alpha-Stim treatment if deemed appropriate by clinician and patient.

			If you want to send a revised flow-chart to help explain then it might be easier.	
13.	29/06/20	**Company** Follow-up questions	Why is the GAD-7 score threshold for starting Alpha-Stim different when GAD is diagnosed by a GP compared to the IAPT pathway?	This has been amended so the threshold is the same for all pathways. Please see attached the revised flow-chart
14.	29/06/20	**Company** Follow-up questions	The company states that a "Practice nurse, health care assistant or company collects Alpha-Stim CES". In what circumstances would the company collect the device from a patient?	This has been removed (please see revised flow-chart) as it was only inserted to allow for Covid-19
15.	29/06/20	**Company** Follow-up questions	Can you confirm whether the economic model presented in your submission is the exact same one as that in the Morriss et al. (2019) paper?	Yes - the economic model is the same one used for the Morriss paper.
16.	09/07/20	**Company** Follow-up questions	RE: iCBT Response rates: 0.542 (0.49-0.59) The point estimate response rate can be found in Gyani et al (2013). Could the company shed some light on how the range for iCBT response was selected?	We used the mean value (0.542). A probabilistic sensitivity analysis using a beta distribution and a modelled 1000 patients were implemented to get a range of outcomes around the mean value
17.	09/07/20	**Company** Follow-up questions	RE: Probability of response to Alpha-Stim 0.47 (0.38-0.48) The point estimate response rate can be found in Morriss et al (2019). Could the company shed some light on how the range for Alpha-Stim response was selected?	We used the mean value (0.47). A probabilistic sensitivity analysis using a beta distribution and a modelled 1000 patients were implemented to get a range of outcomes around the mean value

18.	09/07/20	**Company** Follow-up questions	Table 3 of the company submission states standard practice includes only 8 low intensity (60 min) sessions and 8 high intensity (90 min) sessions. Can the company clarify that standard practice is 8 sessions (guessing this is just a typo in the table)	Yes it's a typo. Standard practice as it was advised by clinical experts was 8 low intensity sessions (60 min)
19.	09/07/20	**Company** Follow-up questions	Could the company provide some details around how the cost per patient of Alpha-Stim device has been calculated? The cost in the company submission is based on a device cost of £450 with 15 patients using it plus additional costs (£70) however in the model, the cost is calculated as £350 with 5 patients using it with no additional costs. While this is also £70 per patient, the EAC need to be clear on the cost of the device to the NHS as well as cost of any additional elements.	Alpha-Stim CES cost per treatment was a manufacturer estimate from the unit cost of the device of £450.00 (excluding valued added tax) with a utilisation of 15 patients over an average product lifetime of 3 years (based on average 10-week sole use per patient). It allowed for losses with respect to the quoted 5- year warranty that was estimated to reduce average product lifetime by 2 years. Additional therapist time, training and consumables was estimated at £40, yielding £70 per duration of the treatment per patient. The breakdown is below; Cost per treatment/patient over lifetime of device £30 per patient Consumables per year (if applicable) and over lifetime of device £10 per patient Maintenance cost per year and over lifetime of device Nil Training cost over lifetime of device £5 per patient Other costs per year and over lifetime of device £25 per patient Total cost per treatment/patient over lifetime of device £70 per patient

20.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Does a proportion of patients on the waiting list drop out before iCBT in standard care (e.g. drugs from GP start to work, patient recovers)? If so, what proportion?	I am unable to ascertain what proportion of patients on the waiting list drop out before iCBT. It would be surprising if there were not some but it appears to be a low proportion. Patients who complete low intensity intervention and turn up for a further assessment are usually committed to treatment and unlikely to improve spontaneously or as a result of treatment from the GP. However,
21.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Are there any important features about the clinical pathway used to treat GAD in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE GAD pathway.	The pathway is largely followed in clinical practice when generalised anxiety disorder is recognised and diagnosed. The main issue is that many patients with GAD are not diagnosed with a mental health condition but as someone with headaches poor sleep etc or are diagnosed with depression when they have GAD.
22.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Does use of Alpha-Stim as an alternative to drug treatment and high intensity psychological interventions after steps 1 and 2 of NICE GAD pathway seem appropriate? These are patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective.	Yes the use of alpha-stim after steps 1 and 2 seems appropriate. These are either patients where step1 or step 2 are ineffective or are refused. Many patients with GAD have recurring problems and have preferences based on past experience.
23.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Would a GP/nurse use the GAD-7 questionnaire to diagnose GAD? What are the approaches for diagnosis of GAD?	The GAD-7 questionnaire is used in some practices but its use in primary care is not common. Instead GAD is diagnosed clinically because of persistent and constant worry that is out of proportion to the stress with a range of other physical and mental symptoms. GPs report lots of patients with both GAD and depression or patients with out of proportion worry with physical symptoms present for much less time than 6 months.

24.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	How is the IAPT pathway for patients with symptoms of anxiety different to non-IAPT? Once referred, do both IAPT and non-IAPT follow the NICE guideline for GAD in the same way? Would IAPT impact the way Alpha-Stim is used?	In the IAPT pathway facilitated self-help low intensity programmes are easy to access and offered routinely. Outside IAPT, self-help programmes for anxiety are available but they are relatively ineffective because the facilitation is rarely available. Patients in IAPT will not be offered the option of antidepressant medication. Patients outside IAPT can rarely access high intensity psychological interventions unless they can pay for them so most are offered medication. Alpha-stim is likely to be offered through primary care rather than IAPT unless NICE approves the technology. The choice in primary care if no progress with education or pure self-help is a choice of IAPT, medication or alpha-stim, and if the person goes through IAPT first they are likely to get low intensity Psychological intervention, then stepped up high intensive CBT before medication or alpha-stim.
25.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Are there any important features about the clinical pathway used to treat social anxiety disorder in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE clinical guideline on social anxiety disorder.	In reality it is very difficult to access psychological treatment for social anxiety disorder through IAPT or any other source. Patients tend to turn to self-help or medication if they consult the health service at all. Therefore the NICE clinical pathway is rarely followed.
26.	09/06/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Would Alpha-Stim be an initial treatment options for adults with social anxiety disorder (see page 19 or NICE clinical guideline on social anxiety disorder) ?	Alpha-stim should not be offered to people with social anxiety disorder unless they also have generalised anxiety disorder as well. There is no evidence based for alpha-stim ion social anxiety disorder.

27.	09/06/20	**EXPERT – Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)**	Other than GAD and SAD pathways are there any other key pathways where Alpha-Stim could be used for the treatment of anxiety disorders?	Many patients in reality have both depression and generalised anxiety disorder. There is evidence for improvement in moderate severity anxiety and depression symptoms but not for depression alone. There is insufficient evidence to support alpha-stim use in other anxiety disorders.
28.	09/06/20	**EXPERT – Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Would Alpha-Stim be a treatment option for people referred to secondary care for anxiety? What does this pathway look like?	GAD is a common comorbidity for many physical and other mental long-term conditions adversely affecting their functional recovery and quality of life. Many such patients might be functionally compromised by drug treatments e.g. loss of alertness so alpha-stim might be a useful adjunctive medication if psychological treatments are ineffective or partially effective. In secondary care mental health services it might be prescribed by community mental health teams and in out-patient settings by mental health professionals skilled in the assessment of GAD. In other long-term conditions there may be a need for an assessment of GAD before alpha-stim or any other treatment for GAD is offered. Most hospitals have such services.
29.	09/06/20	**EXPERT – Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Patient pathway questions	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	GAD may be a temporary condition but it is often oa long-term condition that is never fully in remission for many years. Courses of alpha-stim are likely in reality to be one of a number of treatment options employed when GAD is particularly severe. When it is used in my experience it is often in addition to skills learnt through cognitive behaviour therapy rather than instead of CBT. Once patients have had one or more courses of CBT they rarely gain anything from going through another course of CBT so they use alpha-stim to gain remission from symptoms rather than use drug treatments which might

				become addictive given the recurring nature of GAD. I doubt if there is any data on this but there may be lived experience. Testimonials. At the moment such ways of coping with GAD are only an option for those who can afford it. There is a potentially a major issue in relation to inequalities through lack of income. This disproportionately affects people with long-0term conditions who have limited options for work and therefore cannot afford alpha-stim. Ironically a proportion might be able to work if they could access a treatment that keeps GAD at bay, Data on intermittent but recurrent long-term use (e.g How frequently does it need to be used as a course of treatment? Does alpha-stim lose its effectiveness over time?) may be important because I suspect this is a reality for a substantial proportion of the population diagnosed with GAD, and as a mental health specialist this is what I tend to see in clinical practice
30.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Does a proportion of patients on the waiting list drop out before iCBT in standard care (e.g. drugs from GP start to work, patient recovers)? If so, what proportion?	I do not know the answer to this. IAPT national stats might provide this answer.
31.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Are there any important features about the clinical pathway used to treat GAD in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE GAD pathway.	I do not know the answer to this.

32.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Does use of Alpha-Stim as an alternative to drug treatment and high intensity psychological interventions after steps 1 and 2 of NICE GAD pathway seem appropriate? These are patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective.	Could have after step 1 and after step 1 and 2. Enhancing patient choice is important.
33.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Would a GP/nurse use the GAD-7 questionnaire to diagnose GAD? What are the approaches for diagnosis of GAD?	GAD-7 is a good diagnosis measure for a nurse or other clinician to use. Gaining patient experience is also valuable: asking the degree anxiety is impacting on their lives, functioning and ability to do things they want/need to do.
34.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	How is the IAPT pathway for patients with symptoms of anxiety different to non-IAPT? Once referred, do both IAPT and non-IAPT follow the NICE guideline for GAD in the same way? Would IAPT impact the way Alpha-Stim is used?	IAPT is the pathway for access to psychotherapy, although they do also, bibliotherapy, EMDR, psychoeducation and referral to other/secondary services. As far as I am aware other pathways are GP (who can prescribe meds or refer to IAPT or secondary services) and directly into secondary services. Different services apply NICE guidelines as appropriate to how they are working with individual patient needs and health conditions. IAPT is a good service to adopt Alpha-Stim because it takes a stepped care approach and specifically works with people who present with anxiety.
35.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Are there any important features about the clinical pathway used to treat social anxiety disorder in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE clinical guideline on social anxiety disorder.	I do not know the answer to this.

36.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Would Alpha-Stim be an initial treatment options for adults with social anxiety disorder (see page 19 or NICE clinical guideline on social anxiety disorder) ?	Yes it could be.
37.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Other than GAD and SAD pathways are there any other key pathways where Alpha-Stim could be used for the treatment of anxiety disorders?	Yes, many people who have long term physical health conditions also experience anxiety. These people are often not offered treatment for anxiety. They might not able to attend sessions of psychotherapy (travel issues, cost, commitments [job, caring responsibilities, child care]), and are on many prescriptions meds and so adding more meds might not be best. Some long term conditions (COPD, asthma and diabetes) are interlinked with anxiety (one making other worse) and so treating anxiety may reduce psychical health symptoms. Alpha-Stim could be offered through community nursing services. Due to lack of side effects and good safety record Alpha-Stim could be valuable for anxiety treatment in people under 18.
38.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Would Alpha-Stim be a treatment option for people referred to secondary care for anxiety? What does this pathway look like?	Yes, people could be offered Alpha-Stim when patients are offered other treatments (e.g. psychotherapy, meds). It could be as an alternative to meds or as an addition. It could be as an alternative to psychotherapy, offered whilst on waitlist for psychotherapy, or as an addition (some psychotherapists in the IAPT service where Alpha-Stim was used, used Alpha-Stim together with a course of psychotherapy). Patients referred to secondary care for anxiety could be offered Alpha-Stim and also those referred for other mental illnesses, but who also display symptoms of anxiety.

39.	08/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	No answer provided
40.	25/06/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Patient pathway questions	Telephone call with EAC	Improving Access to Psychological Treatments teams (IAPTs) are the standard structure of service provision for people with anxiety and depression, with similarity in all regions of the UK. Patients are referred to IAPT by their GP or they can self-refer. The economic model's decision tree is broadly aligned to the pathway used in clinical practice. Alpha-Stim could be offered by GP practices as an alternative or in addition to existing treatments and referrals for GAD. Enabling patient choice is an important factor in selection / order of therapies. SSRIs are in very commonplace use. SSRIs are an inexpensive option but are associated with significant side effects for some people and many patients struggle to cease their use i.e. experience withdrawal issues. Based on decades of use, Alpha-Stim CES does not have the side effects associated with SSRIs. Mild tingling on the ears during use has been reported by some patients using Alpha-Stim. The US FDA has recorded no serious adverse events. The cost of Alpha-Stim should consider the purchase cost (c£450) and consumables (c£5 per patient).We will carefully check the sources of costs.

41.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Does a proportion of patients on the waiting list drop out before iCBT in standard care (e.g. drugs from GP start to work, patient recovers)? If so, what proportion?	30-40%
42.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Are there any important features about the clinical pathway used to treat GAD in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE GAD pathway.	No answer provided
43.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Does use of Alpha-Stim as an alternative to drug treatment and high intensity psychological interventions after steps 1 and 2 of NICE GAD pathway seem appropriate? These are patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective.	The main evidence comes from Morriss et al. (2019). The sample size was small (n=169), there was a low uptake of the treatment (only 22% of potentially eligible participants took part), moderate retention rate (70%), and and remission was 45% while 'reliable recovery' (minimal 6 point improvement on PHQ9) was 63%. It's unclear what the rates of uptake, retention and recovery would be in a larger multisite sample.
44.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Would a GP/nurse use the GAD-7 questionnaire to diagnose GAD? What are the approaches for diagnosis of GAD?	Yes
45.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	How is the IAPT pathway for patients with symptoms of anxiety different to non-IAPT? Once referred, do both IAPT and non-IAPT follow the NICE guideline for GAD in the same way? Would IAPT impact the way Alpha-Stim is used?	Patients would be able to purchase the device themselves whether they are referred to IAPT or not, but the device is not currently in the NICE GAD pathway.

46.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Are there any important features about the clinical pathway used to treat social anxiety disorder in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE clinical guideline on social anxiety disorder.	No answer provided
47.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Would Alpha-Stim be an initial treatment options for adults with social anxiety disorder (see page 19 or NICE clinical guideline on social anxiety disorder) ?	Yes, it is a potential initial treatment. However, efficacy and rates of relapse are not known.
48.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Other than GAD and SAD pathways are there any other key pathways where Alpha-Stim could be used for the treatment of anxiety disorders?	No answer provided
49.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Would Alpha-Stim be a treatment option for people referred to secondary care for anxiety? What does this pathway look like?	If there is evidence that the treatment could be an augmentation strategy, then it could be a treatment option for secondary care.
50.	11/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	No answer provided

51.	26/06/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Patient pathway questions	Telephone call with EAC	In the Morriss study only 22% of eligible patients (awaiting iCBT) agreed to join the study and utilise Alpha-Stim, suggesting that patient preference is an important factor. The decision tree model broadly has a good fit with the pathway in clinical practice. It is conceivable that Alpha-Stim could be introduced at an earlier point in the pathway. The model does not include use of drugs. Commonly used drugs e.g. SSRIs could be used at any point in the clinical pathway. However we feel this would impact the model significantly only if there was differential use of SSRIs in patients using Alpha-Stim compared to patients using iCBT. For clinical evidence, randomised studies comparing Alpha-Stim versus sham comparators should provide the most robust evidence. Sham treatments have been given to mimic transcranial direct current stimulation (tDCS) which can provide a sensation to the patient but without delivering the therapy. We note that tDCS is not in the guidance scope for Alpha-Stim. We are advised to consider the duration of improvement of symptoms and also relapse rate following use of Alpha-Stim and iCBT. We are advised to make note of the drop out rate in clinical studies as an indicator of patient tolerance to the therapies. Thank you for referencing the Kennerly paper (2004). We will watch out for the double blind placebo controlled study that the authors planned.

52.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Does a proportion of patients on the waiting list drop out before iCBT in standard care (e.g. drugs from GP start to work, patient recovers)? If so, what proportion?	My impression is there is high dropout of patients in usual care which I would estimate is around a third for both offer of CBT referral or medication and even those initially taking medication I think figures are around a quarter dropout within the first month
53.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Are there any important features about the clinical pathway used to treat GAD in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE GAD pathway.	Reality is that there is very poor follow-up of people with generalised anxiety disorder it is not part of quality and outcome framework and not part of typical general practice therefore people followed up do not go through step to care pathway unless they are under IAPT, again the service has high dropout.
54.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Does use of Alpha-Stim as an alternative to drug treatment and high intensity psychological interventions after steps 1 and 2 of NICE GAD pathway seem appropriate? These are patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2 treatments (low intensity psychological interventions) have not been effective.	Personally I would've thought it could be offered at an earlier part of the pathway as I think it is likely to be more cost-effective than IAPT
55.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Would a GP/nurse use the GAD-7 questionnaire to diagnose GAD? What are the approaches for diagnosis of GAD?	Yes with training – It is not difficult to diagnose especially using questionnaires, primary care nurses have limited mental health experience. Brief half day/1 day training course this would be valuable.
56.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	How is the IAPT pathway for patients with symptoms of anxiety different to non-IAPT? Once referred, do both IAPT and non-IAPT follow the NICE guideline for GAD in the same way? Would IAPT impact the way Alpha-Stim is used?	Patient to do in gauge with IAPT to have some follow-up and could then be stepped up. IAPT Does offer some follow-up therefore likely to have slightly improved recovery rates and treatment as usual. I don't think it would matter if patients have psychological therapy at the same time as Alphastim. I think it will be working at

				different parts of the brain and most of the evidence suggests combination treatments are more effective.
57.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Are there any important features about the clinical pathway used to treat social anxiety disorder in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE clinical guideline on social anxiety disorder.	Social phobia is poorly diagnosed poorly followed up and rarely do we use specific questionnaires in General Practice People in IAPT services I would hope get NICE guidance approach – however I don't recall many patients giving positive recovery stories
58.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Would Alpha-Stim be an initial treatment options for adults with social anxiety disorder (see page 19 or NICE clinical guideline on social anxiety disorder) ?	Yes I think this would be a helpful opportunity and choice for patients
59.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Other than GAD and SAD pathways are there any other key pathways where Alpha-Stim could be used for the treatment of anxiety disorders?	I would be interested in the opportunity around PTSD which I think it's going to be especially relevant post COVID. Also opportunities around panic disorder and mixed anxiety and depression
60.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Would Alpha-Stim be a treatment option for people referred to secondary care for anxiety? What does this pathway look like?	I don't see why there would be a problem with it being used in voluntary sector, primary care or secondary care. In all cases I think it is as simple as explaining how the device is used, providing follow-up and enabling it to be integrated within other pathways.
61.	04/07/20	**EXPERT – Dr David Smart (GP)** Patient pathway questions	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	I have a long-standing interest in common mood disorder And remain surprised that it is not given more priority for intervention and implementation. This especially relates to the opportunity for education and training for frontline staff. Also for the opportunity of regular follow-up and attention step to care pathways and collaborative care

				pathways to be the norm rather than only in a few treatment centres. There is significant opportunity for a physical approach such alphastim to be utilised within medically unexplained symptoms and people with long-term conditions who have more of an attribution of the mental health towards a physical approach
62.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Does a proportion of patients on the waiting list drop out before iCBT in standard care (e.g. drugs from GP start to work, patient recovers)? If so, what proportion?	I am not sure what you are asking here when you say 'drop out before iCBT in standard care'. Do you mean stop attending appointments, or do you mean not respond to invitations to take up iCBT, or do you mean stop following a clinical pathway on their own initiative or on the advice of a clinician. I am assuming you mean stop attending standard care appointments and I would estimate 25-50%.
63.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Are there any important features about the clinical pathway used to treat GAD in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE GAD pathway.	The NICE pathway is a helpful guide but of course it doesn't necessarily reflect local service provision, particular patient and clinician factors and other constraints. Many patients have little enthusiasm with low level interventions and some have been struggling with their symptoms for some time. They have researched a lot of self-help and already accessed low intensity psychological interventions. Talking therapies do not suit everyone by any means and many are averse to using medication.
64.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Does use of Alpha-Stim as an alternative to drug treatment and high intensity psychological interventions after steps 1 and 2 of NICE GAD pathway seem appropriate? These are patients with a diagnosis of GAD for whom step 1 treatment (education and monitoring) and step 2	Yes it seems appropriate to me certainly.

			treatments (low intensity psychological interventions) have not been effective.	
65.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Would a GP/nurse use the GAD-7 questionnaire to diagnose GAD? What are the approaches for diagnosis of GAD?	GAD 7 is a very helpful diagnostic tool but it is best used by an experienced clinician with the confidence to pick up abnormal and severe presentations that may not be detected by questionnaires.
66.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	How is the IAPT pathway for patients with symptoms of anxiety different to non-IAPT? Once referred, do both IAPT and non-IAPT follow the NICE guideline for GAD in the same way? Would IAPT impact the way Alpha-Stim is used?	Alpha-Stim, like IAPT can be used alone and alongside other interventions on the pathway including medication. IAPT would not impact the way Alpha-Stim is used.
67.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Are there any important features about the clinical pathway used to treat social anxiety disorder in real-life practice compared to how it is described in NICE's clinical pathway? Please refer to NICE clinical guideline on social anxiety disorder.	It is rarely practical or necessary to try and distinguish between the anxiety disorders in primary care prior to an IAPT assessment.
68.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Would Alpha-Stim be an initial treatment options for adults with social anxiety disorder (see page 19 or NICE clinical guideline on social anxiety disorder) ?	After assessment, education and a period of reflection on self-help resources. I would not envisage giving anyone a unit on first presentation.
69.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Other than GAD and SAD pathways are there any other key pathways where Alpha-Stim could be used for the treatment of anxiety disorders?	See answer to Q.6

70.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Would Alpha-Stim be a treatment option for people referred to secondary care for anxiety? What does this pathway look like?	Its very difficult to get anybody seen by secondary care mental health services that does not present a degree of risk to themselves or others. I am sure if such a hypothetical situation existed and it had not been tried already alpha-stim would be an option.
71.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Patient pathway questions	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	No
72.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	The company model references 3 models of iCBT: • Standard Practice model that includes 8 low intensity iCBT sessions costing • 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT • Clark and Wells model' with 14 sessions of 90 min sessions of iCBT In your experience, which model is most common? Are they all used in the IAPT service? How do you decide which model of iCBT to use?	Only the standard practice model is used by IAPT.
73.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Would patients be offered a condensed model of iCBT (fewer/shorter) sessions?	In some IAPT services, IAPT may offer 6 or 7 sessions rather than 8 but this is likely to be less severe cases (e.g. GAD-7 score less than 12, no comorbidity or people who have not failed other treatment) than the ones presented in the evidence.

74.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	What proportion of patients who fail first line iCBT take up the second round of iCBT?	IAPT services are very unlikely to offer a second course of iCBT, only if there were administrative or other reasons for not having a full course of iCBT on the first occasion.
75.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Would patients ever be offered a 3rd round of iCBT?	None
76.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	The economic model uses a response rate of 54.2% (range 0.49 – 0.59) for patients treated with iCBT for GAD. Is this a reasonable figure and range?	Yes this is a reasonable range.
77.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Do patients have the same response rate of 54.2% to first and second rounds of iCBT? Please estimate values. Do patients who have iCBT after failing to respond to Alpha-Stim have the same response rate? Please estimate values.	Generally response rates to a second round of iCBT would be very low which is why I have never known IAPT to offer it. Patients who have not responded to Alpha-stim will have a slightly lower response rate to iCBT nearer to 0.50 rather than 0.59.
78.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Are patients who show recovery after the first line of iCBT offered a second round?	Patients are discharged and then usually have to wait 12 months before they are offered another course of IAPT treatment.

79.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Is a response rate to Alpha-Stim (for GAD) of 0.47 (range 0.38-0.48) reasonable?	Yes
80.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	How is recovery or remission from GAD defined? i.e. at which point would treatment for GAD be stopped?	A score of 7 or less on the GAD-7 score is considered remission.
81.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	The economic model uses a cost of £110.96 for a 60 min iCBT and £199.17 for 90 mins. Does this seem reasonable?	Yes
82.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	What proportion of patients with GAD will receive medication? Will this proportion be the same for patients treated with iCBT compared to Alpha-Stim?	Approximately 50% will receive medication, most often antidepressants. There are unlikely to be differences between iCBT and alpha-stim. Some prefer these treatments as an alternative to medication and others are seeking greater effectiveness than medication alone.
83.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	What are the most common drugs and dosages for treating GAD? Are these specific to GAD or are they used to treat depression also?	SSRI antidepressants are most commonly used, sometimes at lower doses than for depression e.g. 50mg sertraline per day and sometimes similar doses as for depression e.g. 100-200mg per day. Some patients take benzodiazepine drugs continuously or more often when needed, others take low dose or similar dose to depression

				tricyclic or SNRI antidepressants. Propranolol I and low dose antipsychotic drugs are still sometimes used and pregabalin or gabapentin increasingly.
84.	08/07/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	What proportion of patients with GAD (at Step 3 of pathway) refuse iCBT? What treatment is used at this point?	10-15% of patients refuse iCBT if they completed low intensity psychological treatment in IAPT and are still symptomatic. At this point patients are referred back to the GP and placed on medication.
85.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	The company model references 3 models of iCBT: • Standard Practice model that includes 8 low intensity iCBT sessions costing • 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT • Clark and Wells model' with 14 sessions of 90 min sessions of iCBT In your experience, which model is most common? Are they all used in the IAPT service? How do you decide which model of iCBT to use?	I do not know the answer to these questions. Please contact IAPT or look for published figures. I think each IAPT service differs in its approach.
86.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Would patients be offered a condensed model of iCBT (fewer/shorter) sessions?	I do not know the answer to this question. Please contact IAPT or look for published figures. I think each IAPT service differs in its approach.
87.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	What proportion of patients who fail first line iCBT take up the second round of iCBT?	I do not know the answer to this question. Please contact IAPT or look for published figures

88.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Would patients ever be offered a 3rd round of iCBT?	I do not know the answer to this question. Please contact IAPT or look for published figures. I think each IAPT service differs in its approach.
89.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	The economic model uses a response rate of 54.2% (range 0.49 – 0.59) for patients treated with iCBT for GAD. Is this a reasonable figure and range?	I do not know the answer to this question. Please look at the reference used to calculate this figure
90.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Do patients have the same response rate of 54.2% to first and second rounds of iCBT? Please estimate values. Do patients who have iCBT after failing to respond to Alpha-Stim have the same response rate? Please estimate values.	I do not know the answer to these questions. Please contact IAPT or look for published figures
91.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Are patients who show recovery after the first line of iCBT offered a second round?	I do not know the answer to this question. Please contact IAPT or look for published figures. I think each IAPT service differs in its approach.
92.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Is a response rate to Alpha-Stim (for GAD) of 0.47 (range 0.38-0.48) reasonable?	Please look at the reference used to calculate this figure

93.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	How is recovery or remission from GAD defined? i.e. at which point would treatment for GAD be stopped?	There are cut off points for the GAD-7 measure used which define recovery or remission
94.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	The economic model uses a cost of £110.96 for a 60 min iCBT and £199.17 for 90 mins. Does this seem reasonable?	I do not know the answer to this question. Please contact IAPT or look for published figures
95.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	What proportion of patients with GAD will receive medication? Will this proportion be the same for patients treated with iCBT compared to Alpha-Stim?	I do not know the answer to these questions. There are probably published statistics available for the first question.
96.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	What are the most common drugs and dosages for treating GAD? Are these specific to GAD or are they used to treat depression also?	I do not know the answer to this question. There are probably statistics available for NHS specific drug prescription for specific disorders.
97.	07/07/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	What proportion of patients with GAD (at Step 3 of pathway) refuse iCBT? What treatment is used at this point?	I do not know the answer to this question. Please contact IAPT or look for published figures

98.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	The company model references 3 models of iCBT: • Standard Practice model that includes 8 low intensity iCBT sessions costing • 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT • Clark and Wells model' with 14 sessions of 90 min sessions of iCBT In your experience, which model is most common? Are they all used in the IAPT service? How do you decide which model of iCBT to use?	No response given
99.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Would patients be offered a condensed model of iCBT (fewer/shorter) sessions?	No response given
100.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	What proportion of patients who fail first line iCBT take up the second round of iCBT?	No response given
101.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Would patients ever be offered a 3rd round of iCBT?	No response given

102.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	The economic model uses a response rate of 54.2% (range 0.49 – 0.59) for patients treated with iCBT for GAD. Is this a reasonable figure and range?	This seems to be a reasonable figure and range
103.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Do patients have the same response rate of 54.2% to first and second rounds of iCBT? Please estimate values. Do patients who have iCBT after failing to respond to Alpha-Stim have the same response rate? Please estimate values.	If the clinical response after the first round of iCBT is limited, then the response after the second round of iCBT is often also limited, but it would be necessary to take into account any factors that might have contributed to the response in the first round. I don't know if there is literature on the response rate to iCBT after failing to respond to Alpha-Stim.
104.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Are patients who show recovery after the first line of iCBT offered a second round?	No response given
105.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Is a response rate to Alpha-Stim (for GAD) of 0.47 (range 0.38-0.48) reasonable?	This seems reasonable based on the literature to date.

106.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	How is recovery or remission from GAD defined? i.e. at which point would treatment for GAD be stopped?	Remission can be defined as no longer meeting diagnostic criteria for the disorder or can be defined as having symptoms which are less than a particular score on a specific rating scale, for example having a score < 7 on the Hamilton Anxiety Rating Scale (HAM-A) or a score of < 5 on Generalized anxiety disorder scale (GAD-7). For remission to be considered to be clinically meaningful, it should also be sustained for a period of time, usually over several consecutive weeks.
107.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	The economic model uses a cost of £110.96 for a 60 min iCBT and £199.17 for 90 mins. Does this seem reasonable?	No response given
108.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	What proportion of patients with GAD will receive medication? Will this proportion be the same for patients treated with iCBT compared to Alpha-Stim?	This depends on what a patient would prefer, if they might prefer iCBT or medication.
109.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	What are the most common drugs and dosages for treating GAD? Are these specific to GAD or are they used to treat depression also?	The most common medication is a selective serotonin reuptake inhibitor (SSRI), which is also used to treat depression. If this isn't effective, then another SSRI can be tried or a serotonin noradrenaline reuptake inhibitor (SNRI) can be tried, which are also used to treat depression. If these are not effective, then pregabalin can be considered, which is not generally used to treat depression.

110.	10/07/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	What proportion of patients with GAD (at Step 3 of pathway) refuse iCBT? What treatment is used at this point?	Patients would be offered a referral to a community mental health team or to specialist services and the treatments could include a combination of medication and psychological therapy or augmentation with medication, assessment of supports and relationships, withing a comprehensive care plan.
111.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	The company model references 3 models of iCBT: • Standard Practice model that includes 8 low intensity iCBT sessions costing • 'Heimberg model' with one session of 90 min iCBT followed by 15 sessions of 60 min iCBT • Clark and Wells model' with 14 sessions of 90 min sessions of iCBT In your experience, which model is most common? Are they all used in the IAPT service? How do you decide which model of iCBT to use?	As a full-time GP working in Nottingham I have little knowledge of the different types of CBT offered by IAPT services. I would have no means of influencing the type of CBT offered to patients as I almost exclusively encourage self-referral in my patients.
112.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	Would patients be offered a condensed model of iCBT (fewer/shorter) sessions?	Don't know
113.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	What proportion of patients who fail first line iCBT take up the second round of iCBT?	Approx. 50% will have another go at CBT
114.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)**	Would patients ever be offered a 3rd round of iCBT?	Very unusually in my experience and always from an alternative provider.

		Questions relating to economic model		
115.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	The economic model uses a response rate of 54.2% (range 0.49 – 0.59) for patients treated with iCBT for GAD. Is this a reasonable figure and range?	Yes
116.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	Do patients have the same response rate of 54.2% to first and second rounds of iCBT? Please estimate values. Do patients who have iCBT after failing to respond to Alpha-Stim have the same response rate? Please estimate values.	I am not able to answer this question with any high degree of confidence but my feeling based on experience is that about half of pateints who dont respond to a first course will respond to a second and I think this will be about the same as pateints who have not responded to Alpha-Stim.
117.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	Are patients who show recovery after the first line of iCBT offered a second round?	Not immediately in Nottingham – usually asked to consolidate for three months.
118.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	Is a response rate to Alpha-Stim (for GAD) of 0.47 (range 0.38-0.48) reasonable?	Yes, in my experience with 50 users
119.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)**	How is recovery or remission from GAD defined? i.e. at which point would treatment for GAD be stopped?	This would not be as simple as attaining a threshold score on GAD-7 for instance. There would need to be a degree of concordance between patient and clinician.

		Questions relating to economic model		
120.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	The economic model uses a cost of £110.96 for a 60 min iCBT and £199.17 for 90 mins. Does this seem reasonable?	I am not able to comment on this.
121.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	What proportion of patients with GAD will receive medication? Will this proportion be the same for patients treated with iCBT compared to Alpha-Stim?	I think an Alpha-Stim option would reduce the proportion of patients prescribed medication and/or using IAPT but I cannot put a figure on it.
122.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	What are the most common drugs and dosages for treating GAD? Are these specific to GAD or are they used to treat depression also?	SRRI antidepressants are the commonest in my experience, predominantly sertraline in a dose range 25-200mg and escitalopram in a dose range 5-20mg. SNRIs such as venlafaxine (37.5mg-300mg) maybe used as second-line or as an alternative an atypical such as mirtazapine (15-45mg)
123.	07/07/20	**EXPERT – Dr Simon Royal (Honorary Assistant Professor Primary Care / GP)** Questions relating to economic model	What proportion of patients with GAD (at Step 3 of pathway) refuse iCBT? What treatment is used at this point?	Few will refuse iCBT if they have not tried it before. Medication would be offered.

124.	02/09/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	If a patient does not respond to Alpha-Stim, what is the possibility/likelihood they will respond to iCBT (and vice versa)	This is unknown from current data. There is no scientific reason to suggest that treatment with alpha-stim would make someone more or less responsive to iCBT if they were given sequentially or vice versa. However, if patients have not responded to many treatments before, then they are less likely to respond to any further intervention (the concept is known as treatment resistance although there is no widely accepted definition for anxiety disorders). It is also possible that those who adhere badly to treatments, whether alpha stim or iCBT, might also find them ineffective. There is a possibility from the data in Morriss et al (2019) that those patients who did badly with alpha –stim in the first 12 weeks and then sequentially had iCBT might do badly. This could be because 6-12 weeks of alpha-stim with minimal benefit makes them unresponsive to iCBT (however 6 weeks of alpha-stim followed by or at the same time iCBT is given within the same 12 weeks was similar in response rate to no CBT), treatment resistance to any treatment or these are patients who do not adhere well to treatment. The design of the study does not allow an assessment of these possibilities. A further analysis of the data in Morriss 2019 just accepted for publication in the Journal of Affective disorders intriguingly suggests that continued improvements in anxiety and depression symptoms at 24 weeks are mediated by alpha stim effects on depression at 12 weeks but at earlier time points they are mediated by improvements with alpha stim on anxiety symptoms in the first four weeks. It is possible that sustained improvements in anxiety with alpha stim might require short-term effects in anxiety and

				more sustained benefits on depression (with alpha-stim or iCBT). However this is a tentative hypothesis.
125.	02/09/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Current published response rates for Alpha-Stim are around 47% and for iCBT are around 54%. From some published evidence, there is a suggestion that the response rate for patients who have both Alpha-Stim and iCBT may be much lower. Based on your clinical judgement and experience, if a patients does not respond to Alpha-Stim is there any reason to suggest that their response to subsequent iCBT would be much lower than 54%?	From my clinical experience with severe and long-standing anxiety, iCBT and alpha-stim are complimentary in terms of keeping anxiety symptoms to a manageable level. Alpha-stim calms the mentation (worrying) and physiological arousal while iCBT gives the person cognitive and behavioural strategies to utilise, particularly when there are exacerbations of anxiety.
126.	02/09/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)** Questions relating to economic model	Could you provide some indication of what response rate might be realistic for patients who have not responded to an initial non-pharmacological treatment such as Alpha-Stim and gone on to receive a second type of treatment such as iCBT?	The response rates would be expected to be similar to iCBT whether or not they responded to alpha-stim. They have different sites of action – CBT on the content and form of negative thinking and behaviour that maintains the anxiety, while alpha-stim has a calming effect on mentation and physiology of the body. However, there is the possibility that those who do not obtain a clinically important change with alpha stim in the first 6 weeks might become unresponsive to iCBT unless it is given immediately. This is not compatible with my clinical experience though.
127.	02/09/20	**EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)**	Could you comment on whether there is anything about non-responders which confound or impact the response rates? For example • Are these patients likely to have more severe symptoms or had symptoms for longer?	Non-responders are more likely to be treatment resistant to multiple types of treatment, and unwilling or unable to use every day for one hour for at least six weeks. Severity of symptoms, failure to improve with one form of psychological treatment, and the severity of initial depression,

<table>
<tr><td></td><td></td><td>Questions relating to economic model</td><td>• Are these patients likely to begin a course of treatment and not complete it for some reason?
• Do some patients deteriorate during non-pharmacological treatments?</td><td>sleep problems or pain do not make alpha-stim less effective. The effects of illicit drugs and alcohol on response of alpha-stim in anxiety disorders is unknown. In previous research, patients did not deteriorate during alpha-stim but this has happened in clinically in the face of a new overwhelming life situation.</td></tr>
<tr><td>128.</td><td>02/09/20</td><td>EXPERT - Prof Richard Morriss (Professor of Psychiatry & Community Mental Health)

Questions relating to economic model</td><td>Specifically in relation to data reported in the publication Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder Morriss et al (2019) we have some queries around the data reported

• Could you please clarify what the recovery rates at week 24 were for:
○ All patients
○ Patients treated with only Alpha-Stim
○ Patients treated with Alpha-Stim +iCBT

1.
Based on the numbers reported in table 3: we calculate the following

<table><tr><td>Treatment</td><td>Total N</td><td>Responders</td><td>Response rate</td></tr><tr><td>All patients (Alpha-Stim alone or with any other treatments)</td><td>161</td><td>77</td><td>47.8%</td></tr></table></td><td>In Morriss et al (2019), recovery rates at 24 weeks:
All patients (n=161), 77 recovered (47.8%)
No CBT (n=81), 53 recovered (65.4%)
Any CBT (n=80), 24 recovered (30.0%)
Alpha stim and iCBT completed together in first 12 weeks, 17 recovered (68.0%)
Stopped or completed alpha stim and then had iCBT, 7 recovered (12.7%). Note number of sessions of iCBT not recorded.</td></tr>
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<tr><td>Alpha-Stim Only (no iCBT)</td><td>81</td><td>53</td><td>65.4%</td></tr>
<tr><td>Alpha-Stim + iCBT (not reported in the paper, calculated from the information provided)</td><td>80</td><td>24</td><td>30%</td></tr>
</table>

However we note that in the text of the publication the following results are reported
<table>
<tr><th>Treatment</th><th>Total N</th><th>Responders</th><th>Response rate</th></tr>
<tr><td>Alpha-Stim Only (no iCBT)</td><td>81</td><td>53</td><td>65.4%</td></tr>
<tr><td>Alpha-Stim + iCBT (not reported in the paper, calculated from the information provided)</td><td>25</td><td>17</td><td>68%</td></tr>
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<tr>
<td>129.</td>
<td>28/08/20</td>
<td>EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)

Questions relating to economic model</td>
<td>If a patient does not respond to Alpha-Stim, what is the possibility/likelihood they will respond to iCBT (and vice versa)?</td>
<td>There are research papers which describe iCBT response rates. There are different iCBT programs and so response rates differ. NICE and Cochrane reviews of evidence can inform answer to this. Morriss’s alpha-stim paper mentions iCBT</td>
</tr>
</table>

130.	28/08/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Current published response rates for Alpha-Stim are around 47% and for iCBT are around 54%. From some published evidence, there is a suggestion that the response rate for patients who have both Alpha-Stim and iCBT may be much lower. For patients receiving iCBT as a second therapy after trying Alpha-Stim but gaining no response, Would you expect a lower response rate from iCBT than the published value 54%?	I suppose it depends on individual reasons for trying Alpha-Stim instead of iCBT if a person had this option. If people chose Alpha-Stim because they did not think iCBT would work or if they did not like the idea of it then this group would be different to those who chose iCBT first and so their response rates could be lower.
131.	28/08/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Could you provide some indication of what response rate might be realistic for patients who have not responded to an initial non-pharmacological treatment such as Alpha-Stim and gone on to receive a second type of treatment such as iCBT?	No
132.	28/08/20	**EXPERT – Dr Chris Griffiths (Senior Research and Evaluation Fellow)** Questions relating to economic model	Could you comment on whether there is anything about non-responders which confound or impact the response rates. For example • Are these patients likely to have more severe symptoms or had symptoms for longer? • Are these patients likely to begin a course of treatment and not complete it for some reason? • Do some patients deteriorate during non-pharmacological treatments?	Re: '• Are these patients likely to have more severe symptoms or had symptoms for longer?' I do not know the answer to this Re: '• Are these patients likely to begin a course of treatment and not complete it for some reason?' yes Re: '• Do some patients deteriorate during non-pharmacological treatments?' this is true for all treatments

133.	09/09/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	If a patient does not respond to Alpha-Stim, what is the possibility/likelihood they will respond to iCBT (and vice versa)?	I would expect that the response rate to iCBT would be around 50%.
134.	09/09/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Current published response rates for Alpha-Stim are around 47% and for iCBT are around 54%. From some published evidence, there is a suggestion that the response rate for patients who have both Alpha-Stim and iCBT may be much lower. For patients receiving iCBT as a second therapy after trying Alpha-Stim but gaining no response, Would you expect a lower response rate from iCBT than the published value 54%?	If the form of the disorder is more of a treatment resistant form, this might be seen clinically as a lower response rate with consecutive treatment trials because it isn't possible to predict clinical outcome before the start of treatment for an individual patient at the present time. If there are distinct mechanisms for Alpha-Stim and iCBT, then I would expect that the response rate for iCBT following Alpha-Stim should be comparable. As there are likely some common mechanisms, such as the therapeutic relationship, as well as distinct mechanisms for Alpha-Stim and iCBT, it isn't clear whether the response rate for iCBT would be much lower.
135.	09/09/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Could you provide some indication of what response rate might be realistic for patients who have not responded to an initial non-pharmacological treatment such as Alpha-Stim and gone on to receive a second type of treatment such as iCBT?	The literature is quite limited for this question. I would expect a comparable response rate.

136.	09/09/20	**EXPERT – Prof Cynthia Fu (Professor of Affective Neuroscience/ Honorary Consultant Psychiatrist)** Questions relating to economic model	Could you comment on whether there is anything about non-responders which confound or impact the response rates. For example • Are these patients likely to have more severe symptoms or had symptoms for longer? • Are these patients likely to begin a course of treatment and not complete it for some reason? • Do some patients deteriorate during non-pharmacological treatments?	Having more severe symptoms is strongly associated with a reduced response rate. Having a longer duration of untreated symptoms is also associated with a reduced response rate. Comorbid disorders and some personality features can also impact on response rates. However, we do not have any clinical predictors at the level of the individual patient at the present time. These are clinical factors that are associated with clinical response. Starting a course of treatment and discontinuing it early could reflect a number of reasons, such as adverse events or personal characteristics, which would affect response rates. Being on a wait list control treatment arm has been associated with a deterioration in symptoms. Some patients do deteriorate during non-pharmacological treatments, and they tend to discontinue the treatment.

Insert more rows as necessary

Appendix 1.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from question 11:

Primary care GP Services

Patient consults GP (or prescribing nurse) face to face or remotely who assesses the patient for anxiety.

↓

GP or prescribing nurse diagnoses Generalised Anxiety Disorder with GAD-7 score ≥8 has functional impairment at step 3 of NICE GAD pathway, offers Alpha-Stim CES as alternative to drug treatment and high intensity psychological treatment after steps 1 and 2 of NICE GAD pathway (step 1, education and watchful waiting 2 weeks, step 2 low intensity psychological intervention offered and not effective or refused by patient).

↓

2.

Practice nurse or health care assistant supplies Alpha-Stim CES and shows how to use (could be via telephone call and video presentation)

↓

Daily use by patient at home for 60 minutes for 6 weeks

↓

Telephone support within 72 hours

↓

3.

Practice nurse or health care assistant collects Alpha-Stim CES. Completes GAD-7. Patient is discharged if GAD-7 score is 7 or below. Patient is signposted to GP if GAD-7 ≥ 8 and in consultation with GP is offered further 6 weeks Alpha-Stim CES if appropriate. If functional impairment then patient may be referred for drug or high intensity psychological treatment.

4.

Primary Care Improving Access to Psychological Treatment (IAPT)

Self-referral or primary care referral.

↓

Generalised Anxiety Disorder diagnosed. Low intensity psychological intervention given. GAD-7≥8 because this is the current IAPT threshold to be offered high intensity psychological treatment. Eligible for high intensity psychological intervention, either on waiting list for high intensity psychological treatment or prefers to have Alpha-Stim CES.

↓

IAPT Psychological Wellbeing Practitioner (PWP) shows how to use Alpha-Stim CES and supplies for 6 weeks

↓

Telephone support within 72 hours

↓

IAPT PWP collects Alpha-Stim CES. Completes GAD-7. Patient is discharged if GAD-7 score is 7 or below. If GAD-7 ≥8 patient is offered further 6 weeks Alpha-Stim CES if appropriate and offered high intensity treatment if on waiting list for it already or offered high intensity if not or discharge to GP.

Secondary care mental health or long-term conditions pathway

Existing patient with serious mental illness or long-term physical condition diagnosed with comorbid Generalised Anxiety Disorder that is impairing function and GAD-7 ≥10 that has not improved with education and simple psychological intervention. Additional medication undesirable e.g. sedation, addiction potential or contraindicated.

↓

Mental health professional or support worker shows how to use Alpha-Stim CES and supplies for 6 weeks

↓

Telephone support within 72 hours

↓

Mental health professional or support worker collects Alpha-Stim CES. Completes GAD-7. Patient stops using Alpha-Stim CES if GAD-7 is 7 or below. If GAD-7 ≥8 patient is offered further 6 weeks Alpha-Stim CES if appropriate, in consultation with mental health professional.

Consider high intensity psychological treatment if GAD-7 score ≥8 and functional impairment.