National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT477 Alpha-Stim AID for anxiety disorders

Consultation comments table

Final guidance MTAC date: 11th December 2020

There were 14 consultation comments:

- The manufacturer submitted 1 comment
- A professional organisation submitted 1 comment
- 3 Healthcare professionals submitted 3 comments
- 9 lay persons submitted 9 comments

The comments are reproduced in full, arranged in the following groups draft recommendations, evidence and patient experience using the technology.

#	Consultee ID	Role	Section	Comments	NICE response
Recommendation (comment 1 to 2)					
1	1	Manufacturer	1.1/1.2	The Alpha-Stim AID represents a safe, clinically proven, and cost effective anxiety treatment option for patients and clinicians within the NHS at a time when there is a desperate need for additional treatments to be made available. Double blinded research has shown that there is a significant clinical effect when using the Alpha-Stim AID device to treat anxiety and recent NHS studies have replicated these clinical improvements in a Primary Care NHS setting, first in IAPT services and more recently , in two separate trials , via GP surgeries.	Thank you for your comments. The committee considered your comment and the additional evidence carefully (see appendix 1 and 2, commentary from the EAC and clinical experts) and considered that further research is needed to demonstrate the mechanism of action using Alpha-stim AID for treating people with anxiety disorders.

				Questions have been raised about the mode of action and I will download several published papers separately that address this issue directly. There is clear evidence of mode of action and an unquestionable safety record that strongly supports the case for routine adoption of the treatment within the NHS. Another challenge in the draft recommendations was around the pathway for the Alpha-Stim treatment. A study carried out in 2020 by Dr Simon Royal at the Cripps Centre in Nottingham used a nurse led Alpha-Stim clinic to offer a cohort of patients the Alpha-Stim AID device to help with their anxiety. 49 patients were offered the device and 47 went ahead which is a 95 percent uptake. The same number of patients (47) were treated using a GP led existing treatment pathway and the clinical and cost results of the two groups were analysed and compared. I will upload a health economics model that highlights the fact that the Alpha-Stim clinic was both clinically effective when compared to an existing GP pathway, with better patient outcomes, and cost effective, with significant savings generated in the nurse led patient group using the Alpha-Stim AID device. Dr Royal comments on the draft recommendation "My main problem with NICE is not that they are obsessed with getting good quality evidence (which is what they should be doing) more that they over focus on comparing one treatment with another and replacing one option with something else - which betrays an almost complete disconnectedness from the realities of managing minor mental health problems. Sure, if you are about to have some chemo and there are two options it is likely that one will be more cost-effective than another. Mental health problems, certainly in primary care, do not behave like that and what works for one person may not work for another with exactly the same symptoms and a third person may get worse.	Thank you for sharing the recent study by Dr Simon Royal. The EAC reviewed the additional evidence and the cost model (see appendix 4). The committee considered the primary care cost model based on the study carefully. It concluded that there could be a potential saving using the device but the model did not reflect the complexity of clinical practice for example medication use was not included . The committee considered your comment about the use of Alpha-stim in primary care and understood the importance of patient choice for the treatment of people with anxiety in primary care and concluded that Alpha-Stim may be a useful additional treatment option if the evidence to demonstrate its mode of action and associated clinical benefits in treating anxiety is generated. New evidence on the device will be reviewed when it is published and changes may be made to the guidance to reflect the evidence base.

				In my opinion NICE sound foolish when they expect someone to be able to prove that Alpha Stim is better than medication which is better than CBT or any other combination. What we should be looking for is non-inferiority (which is what I demonstrated pretty well I think) and balancing risks and benefits including acceptability, accessibility and safety. At the moment we are working in a health service that is under immense strain trying to serve a population facing widespread and unprecedented levels of stress and anxiety. I think NICE should be more nuanced in their assessment under the circumstances and say that while further work is necessary some users have found it extremely helpful and when compared to private therapy or long term prescriptions it is relatively cheap and extremely safe. Dr Royal's study is being written up for publication by the end of 2020 and the study clearly demonstrates that the Alpha-Stim AID is perfectly suited and very well accepted as part of a GP surgery pathway for anxiety patients. A subsequent study run by Dr David Smart as part of the GPA in Northampton has also shown excellent results in a Primary Care GP setting. The Alpha-Stim AID is being offered to patients via a social prescribing pathway. The number of patients opting to use the device are very high and the clinical outcomes again very positive. We are working with David and his team on a training program for other Primary Care teams throughout the country. This will not only cover the practical usage of the device for patients but also how the Alpha-Stim can be easily and successfully implemented into a GP practice with minimal disruption and huge benefits. Another major factor that we want the NICE committee to consider is one of equality. The Alpha-Stim AID is available for people to buy and use at home but there are many people who really want to try the treatment but can't afford to buy their own device and therefore don't get the opportunity. When we first spoke to NICE back in 2014 we were advised we needed to show effectiveness and	Thank you for your comment. The committee acknowledged that the device is not currently available in the NHS, and people may be indirectly disadvantaged not being able to access this as a treatment option. The accessibility of the device was included in the equality consideration in the scope.

				acceptability within an NHS setting. We have now done that in 3 different studies , one of which has been already been published. It seems really unfair to deny patients and clinicians the opportunity to use the Alpha-Stim treatment when we know it is safe, effective and cheap compared to other existing treatment options, especially in a time when demand for anxiety treatments is higher than ever before. Another important consideration in the current climate is that Alpha-Stim AID can be easily used by the patient at home with no face to face interaction with a clinician required. The results are easily monitored using a GAD-7 measurement scale and each device can be used by multiple patients. I believe we have demonstrated in our research a good level of short term efficacy and in the 2019 study by Professor Morriss improvements in anxiety were seen after 12 weeks active treatment and these improvements were largely maintained after a further 12 weeks with no active treatment. This is a very good indicator that patients who use the Alpha-Stim AID in the NHS and get better, will see those positive effects last for a good period of time after their treatment has stopped. The question of which position in the care pathway the Alpha-Stim AID should take for treating anxiety has been answered with Dr Royal's study which clearly shows that the treatment fits perfectly in a Primary Care GP setting, managed by a clinic nurse rather than a GP. This conclusion has been backed up by a subsequent study at the GPA in Northampton where the Alpha-Stim AID has been readily embraced by patients and clinicians in a GP pathway. We have shown that the Alpha-Stim AID is extremely cost effective in two economic models. By introducing the Alpha-Stim AID into the pathway at GP level costs savings can be generated directly at surgery level by using a nurse rather than GP to treat the patients. We	Thank you for you comment. The committee understood the potential benefit of using Alpha-stim AID could reduce hospital visits, but considered that a better understanding of the mechanism of action using Alpha-stim AID for treating people with anxiety disorders and more evidence on the clinical effectiveness compared with current treatments for anxiety are needed.

				have also shown that using Alpha-Stim AID early in a Primary Care pathway can lead to a significant reduction in the number of patients needing a more expensive course of high intensity therapy, producing not only huge cost savings, but also taking pressure off the long waiting lists for this treatment. Looking objectively it is very difficult to understand the case against routine adoption of the Alpha-Stim AID in the NHS. The treatment is safe, cheap, effective and readily accepted by Primary Care GPs already. We are working directly with Dr David Smart to develop a training program for Primary Care and have a proven model ready to go.	
2	2	Patient organisation	1.2	Anxiety UK believes in treatment choice when it comes to the treatment of anxiety disorders. Although psychological therapies and pharmacological therapies help many, some people still require different support. As such we would welcome the further testing of Alpha-Stim in a range of pragmatic, real world settings to develop our understanding of the efficacy of this treatment.	Thank you for your comment.
Evidence on mode of action using cranial electrotherapy stimulation (comment 3)					
3	7	Healthcare professional	Has all of the relevant evidence been taken into account?	The evidence from the early years appears to have been ignored eg Gomez et al (1979) Bit J Psychiatry reported on the use with 28 Heroin addicts who were split into three groups, CES, Sham CES and Placebo control. Over a 10 day period the CES group reduced Heroin intake significantly from 42mg to 12 mg. The Sham CES group reduced their Heroin intake from 42mg to 37mg and the Placebo Control reduced their Herion intake from 42mg to 41mg. There are three other studies on its efficacy with Substance Misuse in the literature. Two other relevant studies in the literature concern the use of CES as a potentiator in traumatised individuals undergoing psychological therapy who are unable to speak about their trauma without using CES and also as a potentiator during surgery so that patients require less anaesthesia.	Thank you for your comments and sharing studies and data on brain activities using the device. The committee considered your comment and additional evidence carefully (see appendix 3, commentary from the EAC and clinical experts). The committee is aware that there is body of evidence indicating that using the alpha-stim device can produce changes in brain physiology that might be relevant to anxiety but there was no robust evidence showing the impact of regular use of Alpha-Stim AID on the brain waves of people with anxiety disorders. Therefore, it concluded that further research is needed to better understand how Alpha-Stim AID affects brain function in people with anxiety disorders.

				1. RECOMMENDATIONS 1.1 Alpha-Stim AID shows promise for managing disorders. If you discuss with clinicians using the Alpha-Stem AID there is demand from clients/patients for alternatives to medication. It is of particular clinical use in the area of Insomnia where peoples anxious thoughts and preoccupations are keeping them awake and inhibiting restorative sleep. The committee is not clear about how the Alpha-Stem AID relieves anxiety symptoms in people with anxiety disorders. It is important to consider its Innovative aspects (para 2.3) and the evidence that using it receives anxiety symptoms (para 3.2). However, despite these positive comments, para 4 states that a better understanding of how Alpha-Stim AID works in people with anxiety disorders is needed. Working with the alpha wave is one of my Specialist Areas of Expertise. The Alpha-Stem is a device that comes under the field of Electro Medicine which uses electrical stimulation to produce desired psycho-physiological effects and has an influence on neuronal communication. One issue for the medical anxiety field is the focus on synaptic activity which is viewed as a chemical reaction involving neuro-transmitters. However, electrical synapses are more important and the electrical and chemical signals that comprise the neural networks are different in their properties and synaptic transmission.	

				Chemical synapsis are slower but exhibit gain but there is no intercellular continuity. Electrical synapsis are quicker and have a strong local effect. There are many new applications in electro medicine that support this eg tDCS (Transcranial Direct Current Stimulation). It is essential to understand the importance of alpha brainwaves. The alpha waveband (8-11HZ) was first described in 1929 by Hans Berger and for many years this was associated with calm relaxation. Parkinson (1973) used alpha wave training, known as EEG Biofeedback to induce relaxation in patients with agorophobia. Difrancesco (2008) found spontaneous alpha wave activity during relaxation. There are studies which show that it correlates with fluency in creative thinking (Bazanova (2007), cognitive and psychomotor peak performance (Hummel et al 2004), plasticity in creative thinking (Bazanova and Aftanas 2007) and self control ability (thatcher 2007 and Bazanova et al 2007). These are all key factors in the cognitive and behavioural control of anxiety. Mountcastle (1992) found that the alpha waveband facilitates the integration of brain activity triggered by sensory stimuli with the activation of the neural images of current or past experience. In this way it reduces some of the blocking of the anxiety response which worsens symptoms in people with anxiety disorders. In 1998 Mountcastle stated that Using brain oscillations has become one of the most important conceptual and analytic tools for the understanding of cognitive processes.	

				Also of relevance is the work of Gasser et al (1985) who found that the alpha-wave has the best test - retest reliability of all brain waves and is an intra individual stable trait. Basar (2011) stated Alpha is one of the fundamental functional operators of the brain for signal processing and communication in the sensory-cognitive field. Barman and Gebber (1993 & 2007) found Alpha operating oscillations are found also in the spinal cord. These five papers are key in supporting our understanding of why the alpha wave is so critical in reducing anxiety symptoms, particularly as it has an influence through the spinal cord, brainstem as well as the brain. Steriade et al (2001) found that the alpha wave is generally considered an index of vigilance or arousal. Basar (2012) pointed out that the core of the brainstem may be viewed as a form of "high command" which constantly receives and controls all information from the external and internal environments. Zambreanu et al (2005) pointed out that there is a role for the brainstem in central sensitisation in humans. It is known that the cognitive- emotional sensitisation that occurs in anxiety, stress, pain and depression involves catastrophizing, kinesiophobia and somatisation. (Meeus and Nijs Clin Rheum 2007). The Alpha-Stem AID CES device works directly through the brainstem and has a critical role in positively influencing neuronal communication and pathways.	

				Pineda (2005) found that rhythmic oscillations in alpha become coherently engaged in transforming perception in to action ... a 10 Hz rhythm reflects the organisation of a brainstem network that governs Sympathetic Nervous System overflow. So the Alpha-Stem AID has a positive impact on the anxiety/fear response ie fight, flight or freeze governed by the Autonomic Nervous System. Research has shown that CES engages the seretonergic (5-HT) raphe nuclei of the brainstem increasing serotonin. Serotonin can act directly to modulate, cognition and emotionality within the limbic forebrain. The involvement of the brainstem, higher and lower cortices and spinal cord are key mediating variables of the beneficial psycho-physiological effects. It has been shown that increasing the alpha wave inhibits pathways to the amygdala and thalamus. Functions of the amygdala include the control fear responses and the formation of emotional memories. It plays a role in the fight or flight response, The thalamus relays motor and sensory signals to the cerebral cortex. Para 4.11 suggests using electroencephalography measures. This is routine in my Clinical practice where I use the EEG to monitor brainwave activity before, during and post the use of the Alpha-Stim AID so that I can check that the individual is likely to be a positive responder and benefit. The patients can see their EEG responses which helps them decide whether or not they would like to use the Alpha-Stim. Kennerly, Richard (2004) QEEG analysis cranial electrotherapy a pilot study. Journal of Neurotherapy (8)v2.	

				I endorse the use of the Alpha-Stim AID for people with anxiety disorders, PTSD and insomnia. I realise the NICE committee was not looking at the latter disorders but they are interlinked in their characteristics. I would be happy to provide EEG data if that were currently required. Dr [redacted] B.Sc.Hons.M.Sc.C.Psychol.C.Sci A.F.B.Ps.S. ([redacted]) FRSM	
Patient experience (comment 4 to 14)					
4	5	Lay person		I have been using the AS for about 5/6 years now, I'm still using the same device and it has 1000s of hour on it. It has made a massive difference to my life. I was severely depressed, my anxiety was through the roof and I ended up with ME. Of all the medications and counselling etc I have had, the AS as well as meditation and yoga have made the most difference. My mum has fibromyalgia and was heading for a wheelchair, the AS gave her back her life and now goes to the gym. It is amazing and should definitely be recommended to suffers of anxiety, stress, depression and those disorders that develop once you have been going through them for years as your body tries to survive. I hope this helps. Thank you	Thank you for your comment and sharing your experience of using the device.
5	3	Healthcare professional		I have been using this device for 10 years, it enabled me to come off anti depression medication which I was on for 20 years and to stay off it. I was prescribed venlafaxine for anxiety and depression and it helped initially, but when I tried to stop the medication the withdrawal was so terrible I had to keep taking it, even though it was no longer helping with my symptoms. When I discovered the alphastim, my symptoms improved so dramatically that I was able to start tapering my meds. It took a very long time to completely stop, but with the help of the alphastim device I was able to quit the venlafaxine and manage my anxiety and depression with the device. I now only need use it in times of stress. The alphastim has helped many of my patients, family and friends too, with none of the debilitating side effects	Thank you for your comment and sharing your experience of using the device.

				or withdrawal symptoms associated with anti depression medication. As a physician I am very worried that the flawed analysis will concern patients and surgeons and will result in a negative effect and confidence on the use of this technology. None of that negative effect I feel is in fact justified when looking at the safety profile, salvage rates gained, and literature available, in an environment which is very badly researched. My suggestion is that NICE starts again, defining the pathways correctly, choosing the right comparator and providing the best pragmatic advice to clinicians about the use of this technology. The current evaluation is not robust, useful and has many flaws. It is not realistic advice and I worry about it remaining published in its current format.	
6	6	Lay person		My 27 year old daughter ahs used Alpha Stm to help particularly with her insomnia relatd to her severe treatment resistant depression since Sept 2019. She uses it daily and it helps enormously with her sleep, so that most days she is able to sleep without using prn medication. Being able to have restful sleep has made a huge difference to her quality of life. She has had no side effects except for a slight thought disturbance, she recalibrated dose of the alphastim and has had no further issues, and knows what she needs to do if it happened again. She would not willingly stop using it. It is one of the few things that have brought her any long term relief. We would be delighted to give you more detailed information.	Thank you for your comment and sharing your daughter's experience of using the device.
7	4	Healthcare professional		I am excited that the Alpha-Stim might become available via the NHS. I have had many people contact me who I feel might have benefitted from using this device but they stopped because they knew they couldn't afford to buy their own device. The current private purchase price is £500 for the AID and £750 for the M with VAT relief. I am hoping NICE will also consider the Alpha-Stim for use as a treatment for fibromyalgia and chronic pain. I started personally to use a microcurrent device, called the Alpha-Stim M, 11 years ago. I had been unable to	Thank you for your comment and sharing your experience of using the device.

				work because of pain and fatigue of fibromyalgia for 20 years. I was so disabled that in 2004 I had chosen the electric wheelchair I was about to buy. The Alpha-Stim made approximately a 40% improvement to my symptoms, additional improvement came from changes to my diet and pacing. I was unable to tolerate medications. The Alpha-Stim improved my sleep, lowered my pain and fatigue, and surprisingly totally took away my 'brain-fog'. I knew after a fortnight that Cranial Electric Stimulation was preventing me having relapses and my symptoms continued to improve over a 9 month period of time. After my success I started a private clinic 10 years ago to help others use the Alpha-Stim because I struggled to get the best from the device even though I am medically trained. I wanted to help others benefit from this device. I trained how to use the device with Dr [redacted] and Dr [redacted] In my clinic I hire out devices for patients to trial before they consider buying a device, or some patients hire a device for a short period of time and stop when they have sufficient improvement. I also offer advice to patients who have bought their own devices online and are struggling to get benefits from it. I specialise in helping people with fibromyalgia and chronic pain though I often treat patients with the co-morbidity of anxiety. In the last year I have had one patient with severe anxiety, she can see some improvement to her condition though her husband has seen a marked improvement. Her anxiety is exacerbated by anything medical such as medical appointments. I think the most significant improvement is that her anxiety did not increase with the lockdown caused by covid 19. A more recent case is someone with fibromyalgia and anxiety. She recently did a 2 month trial with one of my devices and she felt she had seen enough improvement in her symptoms to buy an AID. Her main improvement was improvement in her ability to concentrate. I believe like myself she is likely to improve further over the next few months. I feel the device should reduce or prevent her regular SAD mood experienced in the winter months.	

				I have found approximately 70% of my patients went on to purchase their own device after a trial. I particularly like the Alpha-Stim as patients can use it at home when they need relief, it is portable, and treatment can be altered to the patient's needs. Once the patient is taught the individual protocols needed to reduce their symptoms of pain, insomnia, anxiety, fatigue and/ or brain-fog they have control of when to use it which is empowering for the patient. It is also easier to use than cognitive therapies. For example, a trigger of my symptoms was using the London Underground and I used my Alpha-Stim device whilst traveling on the train. [redacted] HCPC registered Occupational Therapist RCOT and Member of the Medical Advisory Board for FMA UK Tel: [redacted] Webpage: www.[redacted]com	
8	8	Lay person		I suffer from relatively mild but ongoing anxiety, depression and insomnia and take a low dose tricyclic antidepressant. Using Alpha-Stim daily or every two days does bring relief from anxiety and I think helps with depression too. My personal experience is that such disorders need a multi-pronged approach: regular exercise and a balanced lifestyle too are important, but I think Alpha-Stim does certainly make a positive contribution.	Thank you for your comment and sharing your experience of using the device.
9	9	Lay person		I've been using the Alpha Stim M for about a year now. My initial reason for getting it was due to severe anxiety and sleeplessness. I usually use the device at night, just before bed. My preferred use is cranial stimulation via ear clips. I've found that it has the effect of 'balancing' me. As soon as I switch it on, I feel the effects, which are: 1. A sense of relaxation emanating from my brain.	Thank you for your comment and sharing your experience of using the device.

				2. Physical stress noticeably reduced. 3. Sense of wanting to sleep (which, as an insomniac with a long history of neurological treatment, is remarkable). In addition, I have used the sticky pads for physical pain, which I have found it helpful for too.	
10	10	Lay person		I used an Alpha-Stim aid to help with anxiety because I did not want to use any medication. It was easy to use and effective. I found my sleep pattern returned to normal and my anxiety levels were no longer overwhelming.	Thank you for your comment and sharing your experience of using the device.
11	11	Lay person		I have been using the Alphastim for quite some time, mainly for anxiety but also for pain. I cannot take anti anxiety medication but have tried CBT. My situation is a little complicated as I have had numerous brain surgeries and have had a lot of stress factors in my life and initially found that my anxiety increased with the earclips, but I sought advice from the company and started to use the AS trodes on my shoulders instead of using the earclips (so a little further away from my brain) and on a low setting every day. I'm really glad that I persevered as I really do think that the Alphastim has helped me quite significantly and I wouldn't be without it now.	Thank you for your comment and sharing your experience of using the device.
12	12	Lay person		Alpha Stim is a joke. They market this to prey on vulnerable people. It's overtly expensive and modern day quackery. Desperate people will try anything. I know - I'm one of them.	Thank you for your comment.
13	13	Lay person		I do suffer from anxiety, but have had chronic itching causing lumps especially on my head which have driven me to scratch until they have bled. I have been taking antihistamines for years, not always effective. I have been eliminating lots of substances to help stop the itching to no avail. Referred to a hospital dermatologist I was put on a course of a certain antidepressant which he said was known to stop itching. It did work 90% but I didn't want to be on those long-term. I read an article about alpha stim re depression and it mentioned itching as well. Through desperation to find something other than antihistamines and antidepressants and their side effects I decided to try this machine. It was very expensive for me buy, over £600 but I thought it was worth a try. Thank God I did, with use	Thank you for your comment and sharing your experience of using the device.

				of a few times a week it has transformed my itching from antihistamines from 1 to 2 per day to 1 every now and again and also been very good for the anxiety the itching caused me. I know this for fact because at times I have forgotten to use it or take it away with me and the itching /anxiety has returned. I 100% hope other people will be given the chance to use this little , fuss free machine, for whatever they need it for. I don't want to ever be without it.	
14	14	Lay person		Just want to say I used Alpha stim for anxiety on my mum who had dementia and me – I also used for pain relief both applications were non invasive easy to use and successful with no stress attached and no negative impact only good results – it is time the NHS looked to non drug answers to individuals circumstances and saved money long term and stopped people being on drugs ad infinitum and causing other side affects that then need more drugs to address – drug free alternatives are always better than drugs especially of they work It seems it easier to get a dangerous drug approved and used irresponsibly to despatch people - like midazolam with little control or compliance re drug legislation on this class 3 drug abused and used on the elderly with dementia with fatal results ignored when such items as alpha stim and other micro current machines and their benefits ignored in favour of lethal and addictive drugs that often make people worse with side effects ignored by those who prescribe I also used other kit that was way more helpful with zero side affects and distress - acti patch pain relief micro current relatively cheap easy to use and no side affects unlike other pain relief	Thank you for your comment and sharing your experience of using the device.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."

Appendices

Appendix 1: EAC's review of the additional evidence submitted by the company on the mode of action of Alpha-Stim

At the MTAC on 18th September 2020, the committee concluded that a better understanding of how Alpha-Stim AID works in people with anxiety disorders is needed. The committee considered that Alpha-Stim AID's mode of action was uncertain although the clinical experts explained the physiological role of alpha brain waves in mediating feelings of calmness. The clinical experts confirmed that Alpha-Stim AID's mode of action had not been investigated in people with anxiety disorders. The committee was therefore concerned about the plausibility of its therapeutic effect. It proposed that further studies should be done, for example using electroencephalography, to record any acute or longer-term changes in brain waves after using Alpha-Stim AID in people with anxiety disorders.

The company provided 7 studies to demonstrate mode of action. Relevance in the context of mode of action is defined as the effect of Alpha-stim AID on brain wave changes in people with anxiety disorder. The EAC has reviewed the additional evidence and presented a commentary table below. A clinical expert has also provided comments on the relevance of these studies.

Study details	Decision problem	Relevance to mode of action	EAC comments
Taylor et al. (2013) A double-blind, randomised controlled study examining the effects of microcurrent cranial electrical stimulation (CES) therapy on activity in pain processing brain regions in people with fibromyalgia.	**Population:** people with fibromyalgia (n=46). **Intervention:** Alpha-stim device (model not reported) **Comparator(s):** sham device; usual care **Outcomes:** Self-reported pain, functional MRI (fMRI) data on activation in pain processing brain regions. fMRI carried out on 6 patients in each of the device groups.	Participants in the active group reported a greater decrease in average pain scores. fMRI imaging was used to demonstrate blood flow and blood oxygen levels in brain. A significant decrease in the fMRI signal was observed in pain processing regions of the brain.	**Not relevant.** The population is out of scope and outcomes did not relate to anxiety. The study did not examine the effect of the Alpha-stim device on brain wave or brain activity in people with anxiety disorders, or link changes in brain activity to changes in anxiety symptoms.

Heffernan (1996) A double blind EEG study. The study examined microcurrent stimulation applied to the trapezius or ear lobe on brain EEG.	**Population:** included participants were people with pain (75% had some level of auto-immune disease, mainly of a rheumatoid type). All subjects showed slow wound healing, fatigue, and periodic "flare-ups" of joint inflammation, causing restriction in movement of various major joints (n=30). **Intervention:** microcurrent stimulation using the Alpha-stim 100 device was applied to earlobes or to the trapezius using disk electrodes **Comparator(s):** placebo (inactivated device) **Outcomes:** EEG data included a measure of the variation of the frequency components waveform (averaged standard deviations of FFT bandwidths) and a correlation dimension from chaos analysis.	The study reported EEG data and made a before and after comparison using microcurrent intervention applied to the trapezius or ear lobe. The study reported changes in EEG FFTs and correlation dimension, and compared the changes in people who used Alpha-stim and those in placebo group. There was a no significant change in FFT of the EEG in people who used Alpha-stim (ear lobe group). A significant increase in the EEG correlation dimension was observed in people who used Alpha-stim (ear lobe group) compared with those in placebo group.	**Not relevant.** The population is out of scope and outcomes did not relate to anxiety. The study did not examine the effect of the Alpha-stim device on brain wave or brain activity in people with anxiety disorders, or link changes in brain activity to changes in anxiety symptoms.
Heffernan (1995) A randomised study examining the effect of CES on stress response.	**Population:** people with stress seeking medical care (n=20) (50% of people with hypertension and 50% with muscle spasm pain).	The study used physiological measures to evaluate the effect of the Alpha-stim device on stress. Significant changes in outcomes were observed compared to the placebo group.	**Not relevant.** The population is out of scope and outcomes did not relate to anxiety. The study did not examine the effect of the Alpha-stim device on brain wave or

	Intervention: CES stimulation using Alpha-stim 100 **Comparator:** placebo (sham treatment) **Outcomes:** stress response measures included pulse rate, finger temperature, electromyogram and capacitance.		brain activity in people with anxiety disorders, or link changes in brain activity to changes in anxiety symptoms.
Kennerly (2006) PhD thesis. An EEG study examined the effects of CES on the electrical activity of the brain.	**Population:** participants for the study were recruited from undergraduate psychology classes (n=96). **Intervention:** a single 20-minute session with Alpha-stim 100 **Comparator:** no comparator **Outcomes:** range of brain activity including alpha, beta frequency.	The study proposed a total of 24 hypotheses to evaluate the effect of a single-20 minutes CES (0.5Hz or 100Hz) on changes in in the eye closed qEEG brain map, mean current density of voxels in the alpha band and theta band. The study reported that there was a significant increase in alpha relative power with concomitant decreases in delta and beta relative power after using the Alpha-stim device. The study concluded that a single 20-minute session of CES does have a significant effect on brain activity (qEEG and low resolution brain electromagnetic tomography) resulting in activity consistent with decreased	**Potentially of some relevance** The population is out of scope. The brain activity data suggests that a single Alpha-Stim session results in changes consistent with decreased anxiety and increased relaxation. The study did not link changes in brain activity to changes in anxiety symptoms.

		anxiety and increased relaxation.	
Lande & Gragnani (2018) A prospective cross sectional study examining the effect of CES on brain wave changes in people having psychiatric care.	**Population:** active-duty military personnel receiving psychiatric care (n=50) who were mildly depressed, had severe trauma-related symptoms and sleep problems. **Intervention:** a single 20-minute session with Alpha-stim AID **Comparator:** no comparator **Study outcome:** brain wave change (qEEG)	The study found that there was a significant increase in the higher beta frequencies after the single Alpha-stim AID session. There was a significant decrease in the slower wave activity after the 10 minutes using Alpha-stim AID. The study demonstrated changes in the beta region of brain in study population (suggesting an increase in mental alertness, focus and concentration). Participants reported a reduction in distress after treatment (using a validated scale). There was a correlation between the amount of current delivered and brain wave activity between 13-15 Hz and 18-21 Hz.	**Potentially of some relevance** The population is out of scope. The study showed that a single Alpha-Stim session improved distress levels in participants and also changes brain activity. However, the study did not examine the device's effect on anxiety, and the authors did not link changes in brain activity to changes in anxiety symptoms.
Qiao et al. (2015) The study investigated the normalization of the intrinsic functional activity and connectivity in adolescents with Tourette's syndrome	**Population:** adolescents with Tourette's syndrome (n=43). **Intervention:** Alpha-stim stress control device	The study demonstrated a significant reduction in Yale Global Tic Severity Scale after 24-week treatment with Alpha-stim of people with Tourette's syndrome. The study also examined blood oxygenation	**Not relevant.** The population is out of scope and outcomes did not relate to anxiety. The study did not examine the effect of the Alpha-stim device on brain wave or

before and after CES with Alpha-stim.	**Comparator:** no comparator **Outcomes:** Tic severity scores, fMRI data	level dependent (BOLD) fluctuations and intrinsic brain functional connectivity based on resting-state fMRI data. The authors concluded from the fMRI results that the CES treatment may normalise the balance between motor and control portions of the cortico-striato-thalamo-cortical circuit.	brain activity in people with anxiety disorders, or link changes in brain activity to changes in anxiety symptoms.
Smith (1999) The treatment effect of using CES in people with attention deficit disorder (ADD).	**Population:** people who attended outpatient psychiatric clinic with stress related symptoms of anxiety or depression with symptoms of ADD (n=23 including 61% people with GAD). **Interventions:** 3 CES device including Alpha-stim CS device **Comparator:** no comparator **Outcomes:** psychological measures (depression and anxiety scales)	The study examined the effect of CES as non-drug intervention for treating people with attention deficit disorder. The study assessed the treatment effect using psychological measure such as depression and anxiety scale). Three CES devices were used in the study and no subgroup analysis was done.	**Not relevant.** The population is partially within the scope (16 people 61% were with anxiety disorders). The study did not examine the effect of the Alpha-stim device on brain wave or brain activity in people with anxiety disorders, or link changes in brain activity to changes in anxiety symptoms.

Appendix 2: Experts' commentary on the additional studies provided by the company on the mode of action of Alpha-Stim

2.1 Commentary from a clinical expert

Having had a chance to review the 7 papers submitted by the company, I think there is one that stands out and should be considered sufficiently close to the indication for GAD to be considered in scope by extrapolation. The Kennerly thesis sounds as if might be of relevance - the published paper is short of detail. There are studies the company did not include in non-clinical populations under stress and looking at other modalities such as fMRI e.g. Fuesner et al (2012).

The paper that stands out is by Lande and Gragnani (2018). It looked at CES used in 50 admissions to a psychiatric unit with mixed diagnosis mainly a range of anxiety disorders related to trauma and combat with/or depression. Generalised anxiety disorder symptoms would be ubiquitous in such a sample. The main outcome for the CES study is the Subjective Units of Distress Scale (SUDS) developed by Jospeh Wolpe in 1969. It is validated as a state of the moment measure of the emotional symptoms of anxiety and used universally for studies on cognitive behaviour therapy and experimental medicine such as challenge tests in adults and children with anxiety disorders. It is therefore a valid and appropriate measure of the emotional symptoms of generalised anxiety for this type of study design, and what we might predict an improvement in total SUDS score with cranial electrical stimulation if it is an effective treatment. If the SUDS scale had been developed in more modern times it might have been labelled as a scale measuring emotional and cognitive features of anxiety. However in the 1960s and 1970s anxiety disorders were often seen on a continuum with stress and distress. Only with the publication of DSM-III was there a distinction made between anxiety disorders and normal and abnormal adjustment to life stressors. There is the appropriate reduction in the SUDS scale after CES and on the face of it this change in the SUDS is simultaneously reflected in a shift in the percentage beta waves associated with focus and concentration and decreased in slow wave activity reflecting rhythms associated with distress. The findings are compatible with a proposed mechanism of action but they are not conclusive.

Criticisms include that this effect is from a single 20 minute CES session, rather than a course of CES in patients with not just generalised anxiety symptoms. The findings on beta waves etc are likely to be hugely contextual. However, this is one reason studies of EEG are single session studies and so highly controlled because it would be difficult to show a signal over time attributable to CES when there are likely to be many confounders. For instance the amount of beta wave activity is going to be related to the cognitive activities and tasks of the individual not just their experience of anxiety. It is also important to note that these are severely ill patients, not just normal people under light stress as most studies using EEG and CES tend to be. The study is much larger than such studies usually are. In the US, CES is used routinely in military personnel after the Veteran's Administration carried out their own review of the effectiveness of CES (published as a full report and a peer reviewed paper). Hence the authors could carry out this experiment in a naturalistic treatment setting so they availed themselves of the opportunity. Ideally

there would have been a group of matched healthy controls to explore any contextual factors that might have biased the results.

I would argue that from a clinical perspective momentary changes in anxiety which is all that could be related to a mechanism of action like this could never replace more sustained clinical symptom improvement measures. The key question is therefore whether CES improves generalised anxiety disorder symptoms or not and for how long. Evidence on EEG after CES could only ever be mildly supportive or contrary, and not really a basis to support or reject a technology in my opinion.

2.2 Commentary from a clinical expert with special interest and expertise in EEG

I have extensive experience of research into the psychological and physiological mechanisms underlying the symptoms mental disorders. In particular I have extensive experience of research using EEG and brain imaging techniques. I am engaged in use of both EEG and MEG to investigate mechanism of potential therapies for mental disorders, including the use of MEG to investigate the effects of transcranial direct current stimulation (tDCS) on electrical oscillations in the brain. I have no experience of either the clinical use nor the investigation of cranial electro stimulation using the alpha-stim device.

I have examined the seven submitted documents and address the findings relevant to two questions:

- Is the stimulation of alpha oscillations (commonly referred to as alpha waves) in a patient likely to help relieve the symptoms of anxiety?
- Is the alpha-stim device likely to be able to generate alpha oscillations?

In the overview, I provide a brief summary of the relevant findings of each of the studies and present my conclusions. In subsequent sections I provide notes giving greater detail about relevant aspects of each of the seven documents.

Overview

Heffernan (1995) provides statistically modest evidence indicating that a single session of 0.5Hz stimulation using the alpha-stim device produces changes in physiological variables potentially relevant to relief of symptoms related to stress. Although placebo-controlled, the study reported no evidence of statistical superiority of 0.5 Hz stimulation over placebo. It provides no direct evidence regarding relief of symptoms of anxiety, nor any direct evidence that the alpha-stim device either generates or modulates alpha oscillations.

Heffernan (1996) demonstrates that electrical stimulation delivered via either ear-lobes or the trapezius muscle can modify EEG oscillations across a broad range of the frequency spectrum extending from 2 – 30 Hz, but does not directly demonstrate an increase in alpha oscillations nor address the question of therapeutic effects on anxiety symptoms.

Smith (1999) reports an impressive therapeutic effect of three weeks of daily Cranial Electro Stimulation (CES) on symptoms of depression and anxiety and on IQ. Participants were randomly assigned to stimulation via three different stimulation devices. This open-label study lacks blindness thereby weakening the credibility of the immediate post treatment effects, while the possibility of natural remission over 18 months diminishes the credibility of the findings at 18 months. The lack of differences between the three devices employed (and the appreciable differences in characteristics such as wave-form of the stimulating current and magnitude of current delivered) indicates possible lack of a specific benefit of the alpha-stim device compared with other devices. It does not directly address the possible role of alpha oscillations in the therapeutic effect.

Kennerly (2005) is a PhD thesis. It provides a very meticulous report of the investigation performed as part of the student's PhD studies. The data appear to show unequivocal evidence of an increase in alpha power in multiple brain regions following 20 minutes of stimulation at both 0.5Hz and 100Hz. The author reports a very large number of statistical tests. In my opinion, none of the author's three criteria provide a strong protection against type 1 (false positive) error. I therefore regard the statistical validity of his conclusions as dubious. The lack of a sham condition is a serious limitation. Nonetheless, Kennerly's findings are strong justification for further investigation. However, until replicated by independent investigators, I do not consider that these findings provide a compelling demonstration that the alpha-stim device generates alpha oscillations in the brain. This thesis does not report effects on symptoms of anxiety, but infers potential therapeutic benefit based on a thorough review of the literature.

Taylor et al (2013) reports a randomized, controlled, double-blind pilot study of the effects of CES stimulation on activity in brain pain processing regions in individuals with fibromyalgia. fMRI employing a pain induction paradigm was performed before and after 60 minutes CES delivered by alpha-stim device daily for 8 weeks, in 6 individuals who received active CES and 6 individuals who received sham CES. The reporting of the analysis of the fMRI data is seriously deficient. This study does not address the question of effects of CES on alpha oscillations, nor the effects on experience of anxiety.

Quio et al (2015) report a resting state fMRI study of connectivity in the cortico-striato-thalamo-cortical circuit in 8 children with Tourette's Syndrome before and after 24 weeks of CES treatment using the alpha-stim device. The findings might be of interest to researchers investigating innovative ways of assessing connectivity. However the analysis techniques are not sufficiently well established to be credible for the purposes of establishing the mechanism of action of a therapeutic device. Furthermore, the sample size is almost certainly too small to allow confident identification of therapeutic effects. There was no comparison with sham treatment. The study does not address the question of the effect of CES on alpha oscillations nor on anxiety.

Lande and Gragnani (2018) describe a study of EEG measured before and after 20 minutes of CES delivered to a sample of military service personnel, typically with trauma-related symptoms. There was no sham condition. Resting state EGG was measured for 30 seconds before, immediately after, and 10 minutes after the CES delivery. EGG was recorded using a Neurosky system that employs a single dry electrode location over the Fp1 site (forehead overlying the frontalis muscle) with a reference electrode on the ear. Dry electrodes are not usually employed in specialist research investigations of EEG. The Fp1 site is very susceptible to artefacts. The authors report improvement in self-rated anxiety symptoms and a significant increase in beta oscillations, most pronounced in the acquisition 10 minutes after cessation of stimulation. Contrary to the findings of Kennerly, they observed a weakly significant reduction in alpha power at 10 minutes. The investigation of the 'eyes-open' compared with the 'eyes-closed' condition employed by Kennerly, together with the use of a single dry electrode overlying frontalis possibly contribute to the differences between the findings of the two studies.

Overall, these studies do provide a diverse body of evidence indicating that CES using the alpha-stim device can produce changes in brain physiology that might be relevant to anxiety. However the diverse range of techniques employed and the questionable quality of the techniques, including the questionable validity of the statistical techniques in some studies, makes it very difficult to draw confident conclusions. With regard to the question of whether or not the alpha-stim device is likely to be able to generate alpha oscillations, the most informative study is that of Kennerly. Despite my concern about validity of the statistical procedures and also the lack of a sham condition, I consider that the reported findings are strong justification for further investigation.

Overall, I do not consider that these 7 documents provide compelling evidence that the alpha-stim device generates alpha oscillations.

The reported studies do not directly address the question of whether the stimulation of alpha oscillations in a patient is likely to help relieve the symptoms of anxiety. Nonetheless, in the introduction and/or discussion sections, several of these documents refer to the plausibility of a therapeutic effect of enhancing alpha oscillations based on other studies. A large body of evidence indicates that increase in mental arousal is associated with reduction in alpha oscillations. Furthermore some evidence indicates that alpha oscillation serve to inhibit activity in brain circuits in a variety of different circumstances. I consider that it is plausible that enhancing alpha oscillations might have a therapeutic effect on anxiety, and that further investigation is fully justified. However, I do not consider that the existing evidence is compelling.

Notes on relevant features of each of the seven studies.

Heffernan 1995.

Twenty people experiencing stress were recruited from the investigator's private practice; half suffered muscle tension and half suffered hypertension exacerbated by stress. 0.5Hz stimulation was delivered in a single 20 minute treatment session; patients were randomized 50/50 to active CES v sham; multiple potentially relevant physiological measures were performed. Significant ($p<0.05$) changes between pre and post treatment observation were reported for several potentially relevant measures. There was no correction for multiple comparisons. There were changes, albeit of lesser magnitude, in the placebo group in some measures (e.g. heart rate and electrical capacitance between the electrodes, significant at $p<0.05$). The 2 way analysis of variance (treatment group by time) was not reported and therefore we cannot conclude that pre- to post-treatment changes were significantly greater in the treatment v sham group. Thus the statistical support for potentially relevant physiological effects is weak. There was no report of changes in symptoms.

The investigator did not explicitly measure of effect on EEG oscillations. The author states that he has demonstrated that 0.5Hz stimulation produces an increase in alpha band power, but provides no data on this nor provides adequate reference to published findings.

Conclusion: This study provides statistically modest evidence indicating that a single session of 0.5Hz stimulation using the alpha-stim device produces changes in physiological variables potentially relevant to relief of symptoms related to stress. Although placebo-controlled, the study reported no evidence of statistical superiority of 0.5 Hz stimulation over placebo. It provides no

direct evidence regarding relief of symptoms of anxiety. This study does not provide direct evidence that the alpha-stim devise either generates or modulates alpha oscillations.

Heffernan 1996

30 individuals were selected from patients in the investigator's pain clinic were randomised to receive electrical active stimulation at 0.5 cycles per sec delivered using an alpha-stim device via electrodes attached to ear-lobes (10 subjects); trapezius muscle (10 subjects) or sham stimulation (10 subjects) for a period of 10 minutes. EEG was measured in 2 minute time windows before and after the 10 minutes of treatment. Analysis of the EEG demonstrated greater smoothing of the fluctuations in EEG power in frequency windows ranging from 2 to 30 Hz after treatment delivered via the trapezius electrodes relative to the placebo condition. Furthermore an analysis of temporal autocorrelation of the EEG signals demonstrated a greater increase a correlation measurement claimed to reflect a healthier brain state, from pre- to post treatment conditions in both the ear-lobe and trapezius stimulation conditions relative to the increase observed in the placebo condition. This study demonstrates that stimulation via electrodes located on both the trapezius muscle and ear-lobes produces potentially beneficial changes in brain oscillations. The effects seen after stimulation at the trapezius sites indicates that very low strength electrical currents can be conducted effectively from the trapezius sites to the brain. In this study, the stimulation of the trapezius has greater effect that stimulation applied to the earlobes. This study does indicate that electrical stimulation modulates brain oscillations but does not demonstrated preferential effects on alpha oscillations compared with other frequencies in to range 2 to 30 Hz.

Indirect evidence of relevance of the findings to the relief of anxiety is based on the claim that abnormality of oscillations in the 5-12 Hz band are observed in anxiety disorders. The only explicit reference to published literature on the therapeutic effect of smoothing of EEG oscillations provided in this paper by Heffenan is to a report regarding neurofeedback treatment for ADHD by Lubar (1995) which I was unable to access. The relationship between EEG oscillations in diverse frequency bands and emotional activity, including anxiety, has continued to be a topic of investigation. (See for example https://doi.org/10.1016/j.neuroimage.2018.05.059) The findings are complex. In my opinion, the claim that smoothing of EEG oscillations is therapeutic for anxiety is plausible but remains speculative.

Conclusion This study does demonstrate that electrical stimulation delivered via either ear-lobes or the trapezius muscle can modulate EEG oscillations across a broad range of the frequency

spectrum extending from 2 – 30 Hz, but does not directly address the question of therapeutic effects on anxiety symptoms.

Smith 1999

23 people (age range 9 to 56) with ADHD symptoms together anxiety and/or depression, were randomly allocated to one of three CES devices each employing different stimulation procedures, 45 min daily for three weeks. Seven were allocated to stimulation via the alpha stim device, with a stimulation current of .6 mA. There were no significant differences in effects of interest between the three devices; results of tests were therefore pooled. Comparison of clinical features post v. pre-treatment revealed significant reduction in IPAT depression and both State and Trait anxiety, and increase in IQ (full scale IQ increased 14 points). Lack of placebo and no blinding seriously weaken the credibility of the findings. 18/23 cases were followed up at 18 months. The therapeutic effects seen immediately post treatment were maintained at 18 months. The authors did not provide an account of treatment in the Follow-Up period or discuss anticipated effects of the passage of 18 months. However the fact that the initial assessment was performed around the time of entry to the clinic with a stress related illness raises the possibility that the mere passage of time would have resulted in remission of symptoms.

Overall: An impressive effect on symptoms of depression and anxiety and on IQ but open label study design and lack of blindness weakens credibility of the immediate post treatment effects while the possibility of natural remission over 18 months diminishes the credibility of the findings at 18 months. The lack of differences between the three devices (and the appreciable differences in characteristics such as wave-form and current delivered) provides no evidence indicating a specific benefit of alpha-stim compared with other devices.

Kennerly 2006 (PhD thesis, approved by examiners, but findings apparently not reported in a peer reviewed publication)

CES was delivered in a single 20 minute session using an alpha-stim device; CES at 0.5 Hz in 38 participants; CES at 100 Hz in 34 participants. EEG was recorded immediately before and immediately after the CES session. No sham condition was employed. The qEEG paired t-tests (post v pre treatment): at both frequencies of CES was associated with significant ($p<.05$) increase in alpha relative power with concomitant decreases in delta and beta relative power. The 0.5 Hz CES was associated with decreases in a wider frequency range of delta activity, while the 100 Hz CES was associated with decrease a wider frequency range of beta activity. Loreta analysis

demonstrated significant changes in alpha in all brain regions. Kennerly claimed that the reported effects are consistent with reduction in anxiety based on reports in literature.

Kennerly provides a meticulous discussion of the complexities of EEG analysis, including a detailed proposal for avoiding type 1 error (drawing false conclusion that an effect of interest is statistically significant) when a very large number of tests are performed. He proposes that type 1 error is unlikely of at least two of three criteria are satisfied. His three criteria are:

1)Similar effects at 0.5Hz and 100Hz. This is dubious because studies of clinical effects indicate both similarities and differences between effects at these two frequencies and therefore one might expect both similarities and differences in effects on EEG.

2) Similar effects using difference montages. Kennerly claims that different montages provide independent tests of his hypotheses. However, different montages reflect different combinations of the same primary data. A spurious effect might be manifest as a consistent effect in different montages

3) Consistent patterns across multiple electrode sites. While this might protect against truly random errors, systematic noise might produce systematic patterns of spurious signals.

He reports a very large number of statistical tests As far as I can see, none of his three criteria provide a strong protection against type 1 error. I therefore regard the statistical validity of his conclusions as dubious. Nonetheless, despite my misgivings about his statistical procedures, the data appear to show unequivocal evidence of increase in alpha power in multiple brain regions following 20 minutes of stimulation at both 0.5Hz and 100Hz. The lack of a sham condition is a serious limitation.

The findings are strong justification for further investigation. However, until replicated by independent investigators, I do not consider that these findings provide a compelling demonstration that the alpha-stim device generates alpha oscillations in the brain. This thesis does not report effects on symptoms of anxiety, but infers potential therapeutic benefit based on a thorough review of the literature.

Taylor et al 2013

A randomized, controlled, double-blind pilot study of the effects of CES stimulation on activity in brain pain processing regions in individuals with fibromyalgia. fMRI during a pain induction paradigm was performed before and after 60 minutes CES delivered by alpha-stim device daily for 8 weeks, in 6 individuals who received active CES and 6 individuals who received sham CES. The reporting of the analysis of the fMRI data is seriously inadequate. There is no statement regarding whether the analysis was a fixed effects or random effects analysis. Two groups of 6 participants is very unlikely to be an adequate sample to detect effects of interest in a random effects analysis. If fixed effects analysis was performed, the effects might reflect idiosyncratic effects occurring in a very small number of individuals. There was no report of a statistical comparison between the two groups. Potentially relevant changes from pre to post treatment scanning session were reported in areas engaged in pain processing in the group receiving active CES. The regions were not defined precisely a priori. The authors do not report an attempt to identify regions of the brain which exhibited significant activation during the pain induction procedure at baseline. Cluster extent criteria were applied when testing for pre- post changes but these criteria were not reported.

Overall, the reporting of the analysis of the fMRI data is seriously deficient. This study does not address the question of effects of CES on alpha oscillations, nor the effects on experience of anxiety.

Quio et al 2015

The authors report a resting state fMRI study of connectivity in the cortico-striato-thalamo-cortical circuit in 8 children with Tourette's Syndrome before and after 24 weeks of CES treatment using the alpha-stim device.

One of the major challenges in resting state fMRI is removing the correlations between BOLD signals induced by movement. This might be expected to be especially challenging in children with Tourette syndrome. The authors do not discuss this issue. They do not report using any the various stringent approaches to removing the influence of movement on fMRI (BOLD) signals that have been developed in the past 15 years. While stringent correction for movement artefacts is crucial for conventional functional connectivity analyses, it is noteworthy that Quio et al use two different analysis procedures which might possibly be less influenced by movement. They employ a sophisticated approach based on independent component analysis and also a Granger connectivity analysis.

The ICA based approach allows the possibility that components that are dominated by movement effects might be separated for components of interest reflecting correlated brain activity. However this remains speculative, and is not discussed by the authors. The particular ICA approach employed by the authors is innovative and might be of interest to investigators developing techniques for assessing brain connectivity, but it is not sufficiently well established to be regarded as credible for purposes of establishing the mechanism of action of a therapeutic device.

Granger causality analysis might perhaps be less subject to movements than conventional resting state functional connectivity analysis insofar as the Granger analysis assesses the temporally delayed influence of one brain region on another. Movement related corrections between BOLD signal in different brain regions would be expected to be most strongly manifest as correlations of coincident brain activity. However the validity of application of the Granger procedure to BOLD data still remains a topic of debate.

Overall, these findings might be of interest to researchers investigating innovative ways of assessing connectivity. However the analysis techniques are not sufficiently well established to be credible for the purposes of establishing the mechanism of action of a therapeutic device. Furthermore this study does not address the question of the effect of CES on alpha oscillations nor on anxiety. The sample size is almost certainly too small to allow confident identification of therapeutic effects. There was no comparison with sham treatment.

Lande and Gragnani 2018

This paper describes a study of EEG measured before and after 20 minutes of CES delivered to an opportunistic sample of military service personnel, typically with trauma-related symptoms. There was no sham condition. Resting state EGG was measured for 30 seconds before, immediately after and 10 minutes after the CES delivery. EGG was recorded using a Neurosky system that employs a single dry electrode location over the Fp1 site (forehead overlying the frontalis muscle) with a reference electrode on the ear. Dry electrodes are not usually employed in specialist EEG research investigations. The authors refer to two conference proceeding that report on the quality of data obtained with the Neurosky system. They also refer to a study of test retest reliability of this system, which reported fair reliability (ICCs 0.57-0.85) for EEG obtained during eyes-open paradigms, and advised use of the signal quality metrics provided by the system in interpreting the data. Lande and Gragnani do not report use of the signal quality metrics. They do report using software which minimizes eye movement and muscle artefacts, but do not report

on the proportion of data excluded on the basis of artefacts. In the penultimate paragraph the authors ‘acknowledge that balancing clinical use and scientific rigour is not perfect’.

They report improvement in self-rated anxiety symptoms and a significant increase in beta oscillations, most pronounced in the acquisition 10 minutes after cessation of stimulation. Contrary to the findings of Kennerly, they observed a weakly significant reduction in alpha power at 10 minutes. The investigation of the ‘eyes-open’ compared with the ‘eyes-closed’ condition employed by Kennerly, together with the use of a single dry electrode overlying the frontalis muscle possibly contributes to the differences.

Appendix 3: EAC and expert commentary on consultee comment (comment 3) re mode of action of Alpha-Stim AID

3.1 EAC review

The EAC reviewed and attempted to identify all of the studies referenced in the comment. For those which were identified, all but one study were not considered to be relevant to the decision problem of Alpha-Stim AID as a treatment for anxiety disorders. Please see the table below for details of the individual citations. One published study (Kennerly 2004) was considered to be relevant to the question of the mode of action of Alpha-Stim in the treatment of anxiety.

Citation (in order that they appear in consultee comment)	Full reference	Relevance
Gomez et al. (1979) Brit J Psychiatry	Gomez E, Mikhail AR. (1978) Treatment of methadone withdrawal with cerebral electrotherapy (electrosleep). Br J Psychiatry. 134: 111– 113	Not relevant to the treatment of anxiety
Difrancesco (2008)	Difrancesco MW, Holland SK, Szaflarski JP. Simultaneous EEG/functional magnetic resonance imaging at 4 Tesla: correlates of brain activity to spontaneous alpha rhythm during relaxation. J Clin Neurophysiol. 2008 Oct;25(5):255-64	Not relevant to Alpha-Stim or anxiety.
Bazanova (2007)	Bazanova, O. M., & Shtark, M. B. (2007). Biofeedback in optimizing psychomotor reactivity: I. Comparison of biofeedback and common performance practice. Human Physiology, 33(4), 400-408.	Not relevant to Alpha-Stim or anxiety.
Hummel et al. (2004)	Closest match: Hummel, F. , Celnik, P. , Giraux, P. , Floel, A. , Wu, W. H. , and Gerloff, C. , et al. (2005). Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain, 128(Pt 3), 490–499	Not relevant to Alpha-Stim or anxiety.
Bazanova and Aftanas (2007)	Bazanova OM, Aftanas LI. [Individual alpha activity of electroencephalogram and nonverbal creativity]. Ross Fiziol Zh Im I M Sechenova. 2007 Jan;93(1):14-26. Russian. PMID: 17465270.	Not relevant to Alpha-Stim or anxiety.
Thatcher 2007 and Bazanova et al 2007	Not found	Relevance cannot be assessed
Mountcastle (1992)	Not found	Relevance cannot be assessed

Mountcastle (1998)	Mountcastle, V. B. (1998). Perceptual neuroscience: The cerebral cortex. Harvard University Press.	Not relevant to Alpha-Stim.
Gasser et al (1985)	Gasser, Theo, Petra Bächer, and Hans Steinberg. "Test-retest reliability of spectral parameters of the EEG." Electroencephalography and clinical neurophysiology 60.4 (1985): 312-319.	Not relevant to Alpha-Stim or anxiety.
Basar (2011)	Closest match: Başar, E. (2012). A review of alpha activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. International Journal of Psychophysiology, 86(1), 1-24.	Not relevant to Alpha-Stim.
Barman and Gebber (1993 & 2007)	Barman, S. M., & Gebber, G. L. (1993). Lateral tegmental field neurons play a permissive role in governing the 10-Hz rhythm in sympathetic nerve discharge. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 265(5), R1006-R1013. Barman, S. M., & Gebber, G. L. (2007). Role of ventrolateral medulla in generating the 10-Hz rhythm in sympathetic nerve discharge. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 293(1), R223-R233.	Not relevant to Alpha-Stim or anxiety.
Steriade et al. (2001)	Steriade, M. (2001). Impact of network activities on neuronal properties in corticothalamic systems. Journal of neurophysiology, 86(1), 1-39. Steriade, M., Timofeev, I., & Grenier, F. (2001). Natural waking and sleep states: a view from inside neocortical neurons. Journal of neurophysiology, 85(5), 1969-1985.	Not relevant to Alpha-Stim
Basar (2012)	Başar, E. (2012). A review of alpha activity in integrative brain function: fundamental physiology, sensory coding, cognition and pathology. International Journal of Psychophysiology, 86(1), 1-24.	Not relevant to Alpha-Stim
Zambreanu et al (2005)	Zambreanu, L., Wise, R. G., Brooks, J. C., Iannetti, G. D., & Tracey, I. (2005). A role for the brainstem in central sensitisation in humans. Evidence from functional magnetic resonance imaging. Pain, 114(3), 397-407.	Not relevant to Alpha-Stim

Meeus and Nijs Clin Rheum 2007	Meeus, M., & Nijs, J. (2007). Central sensitization: a biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome. Clinical rheumatology, 26(4), 465-473.	Not relevant to Alpha-Stim or anxiety.
Pineda (2005)	Pineda, J. A. (2005). The functional significance of mu rhythms: translating “seeing” and “hearing” into “doing”. Brain research reviews, 50(1), 57-68.	Not relevant to Alpha-Stim or anxiety.
Kennerly (2004)	Kennerly, R. (2004). QEEG analysis of cranial electrotherapy: a pilot study. Journal of Neurotherapy, 8, 112-112.	Relevant (see below for details)
Presentation slides were kindly provided to NICE by the consultee, and further information about the study provided by email.	An Evaluation of the Use of Cranial Electrotherapy Stimulation in the Alleviation of Anxiety Disorders (By Lesley Parkinson & Alan Parkinson). Brainhealth, London. EABCT – Geneva (2012). PRESENTATION SLIDES.	Relevant (see below for details)

Kennerly (2004) was considered to be relevant to the issue of mode of action of the Alpha-Stim AID device in the treatment of anxiety disorders.

Kennerly (2004) – published paper

This is a published pilot study to determine the effect of CES on brain activity. Details are as follows:

- **Population:** 30 research volunteers (no further information provided)
- **Intervention:** a single 20 min session with Alpha-Stim 100 (0.5 Hz)
- **Comparator:** None
- **Outcomes:** Digital EEG, blood pressure, heart rate, electrodermal activity and, finger temperature was acquired during a baseline condition, during CES immediately after electrotherapy, and after three weeks of daily use of cranial electrotherapy.

It is unclear whether the findings are based on data collected after a single CES session or after 3 weeks of daily use. Significant increases were seen across the entire cortex in delta and gamma frequencies. Decreases were seen in delta and theta frequency activity with concomitant significant increase in alpha activity. The author reports the following “the study volunteers generally reported feeling more relaxed after 20 minutes of CES. Some volunteers reported feeling as if their head had cleared and they felt more awake. Research volunteers who reported pain or anxiety before the single session of CES treatment reported significant reductions in pain and anxiety after the 20-minute treatment”.

This study has some relevance to the question of the mode of action of Alpha-Stim given that it reports changes in EEG data and patients report feeling less anxious after Alpha-Stim treatment. However, the population is not described and does not appear to have a diagnosis of anxiety.

The consultee also provided further data from a pilot study and a case report based on own clinical practice. Further details of these two studies are provided below.

A pilot study was presented at a conference (2012) (the abstract was published as conference proceeding)

The consultee shared the conference presentation slides. Details are as follows:

- **Population:** 16 participants complaining of stress or anxiety (not on medication). All participants had been referred to the author's clinic with a diagnosis of anxiety disorder.
- **Intervention:** Alpha-Stim for 2 months home use, 20 minutes per day
- **Comparator:** None
- **Outcomes:** Depression, Anxiety & Stress Scale (DASS) and CNS monitoring measured at 3 time points (T1: time of referral to clinic; T2: 4-week period on waiting list; T3: is an assessment made after using Alpha-stim device for 2 months).

The authors report that participants showed a significant increase in alpha-wave activity (mean alpha-wave amplitudes: 3.71 at T1, 4.23 at T2, 6.52 at T3; change from T2 to T3 is statistically significant $p<0.05$) and a significant reduction in self-reported measures of anxiety (15.6 (severe) at T1, 15.2 (severe) at T2, 8.2 (mild) at T3; change from T2 to T3 is statistically significant $p<0.01$) and stress following treatment with Alpha-Stim.

This study is relevant to the question of the mode of action of Alpha-Stim in relation to anxiety. It links brainwave activity (increase in alpha-wave activity) to a reduction in perceived anxiety symptoms.

The EAC note that this is a small, pilot study which was published as an abstract in conference proceedings. As such, the full details of the study have not been reviewed and the study has not been critically appraised.

A case report (2020)

The consultee kindly provided brainwave activity data and linked commentary from a person treated with Alpha-Stim. The patient has been diagnosed with generalised anxiety disorder.. The patient developed GAD following a traumatic experience. She tried to help herself at home through her own research, and was treated with cognitive behavioural therapy and other complementary therapies. The patient started using Alpha-Stim from September 2020 and was advised to use it for 20 minutes per day in the evening or shortly before going to bed.

In the case report, measurements were taken before, during, and immediately after 20 minutes of Alpha-Stim treatment at the beginning of a course of treatment and then 35 days later when the person had been using the device daily for 20 minutes. The consultee concluded that "at both sessions it was demonstrated that the use of the Alpha-Stim CES device had led to an increase in alpha wave calming activity and to a decrease in the fast wave associated with stress, hyper vigilance and hyper arousal".

The EAC note that the report may be of some relevance to the question of the mode of action of Alpha-Stim, however it is an unpublished, non-peer reviewed single case report which should be interpreted with a high degree of caution. Such results are at very high risk of bias and their generalisability uncertain. Such a study is not able to demonstrate the clinically effectiveness of Alpha-Stim.

3.2 Commentary from a clinical expert with special interest and expertise in EEG

The pilot study (n=16) and the case report are both consistent with a large amount of evidence that a least some individuals report a substantial reduction in symptoms of anxiety fowling alpha stim treatment. With regard to the mechanism, in both studies there was an increase in alpha oscillations following treatment. These reports are consistent with the report by Kennerly in his PhD thesis, though at least partially contrary to the paper published by Lande and Gragnani (20180 who reported increase in beta oscillations and decrease in alpha. As discussed in my commentary on Kennerly and on Lande and Gragnani, it is plausible that the use of the dry electrodes in the eyes open condition in the study by Lande and Gragnani contributed to the difference between the studies. Nonetheless, the discrepancy emphasizes that crucial importance of the quality of the EEG data and the circumstances under which it is acquired. Neither Kennerly nor Lande and Gragnani, nor the pilot study and the case study reported by the consultee, reported comparison with a sham condition.

Overall, on the basis body of evidence provided, I think it is plausible that the mechanism of action of alpha-stim in the treatment of anxiety does include the enhancement of alpha oscillations. I certainly think that further investigation, preferably in studies that include a sham condition, is well justified.

Appendix 4: EAC addendum report: primary care cost model

MT477 Alpha-Stim AID for anxiety disorders

Assessment Report Addendum for primary care pathway modelling

- **Produced by:** Cedar
- **Authors:** Megan Dale, Judith White, Susan O'Connell
- **Date completed:** 2nd December 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.

The clinical evidence assessment was submitted to NICE previously on the 14th August 2020, but is included in this addendum for ease of reference, as this clinical evidence provides the inputs for the primary care economic model.

Clinical evidence submitted by the company

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) 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 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] (p[redacted]). • Control: Baseline GAD-7 was [redacted], after treatment was [redacted] (p[redacted]) • No adverse events were reported. [redacted]. • [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 because [redacted], the Alpha-Stim pathway represents a [redacted] but [redacted] are discussed and this [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] reported in preliminary results. • Devices loaned to clinic by company.

Conclusion for clinical evidence

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 high risk of bias based on the currently available information of the study methodology. Only young people, [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] details were reported in the preliminary results and it is therefore not possible to comment on whether the use of Alpha-Stim in this setting would be cost saving. 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.

Economic evidence

Disclaimer

The model was submitted during the consultation period, and the EAC have not had the opportunity to carry out the full critique that would normally be applied to an MTEP economic submission. The company submitted a short report with the model, however this does not contain the full description of the economic model that is normally included in the manufacturer submission.

The EAC have identified some model assumptions, recreated the key calculations, carried out stress testing procedures, briefly reviewed evidence used for clinical inputs and provided some additional sensitivity analysis in the form of threshold diagrams and two-way sensitivity tables. The EAC have not checked either the model calculations or the inputs with the level of detail that would normally be used for this process. Due to time constraints the EAC have limited reporting to a critique of the model as it was submitted. Any uncertainties that the EAC have identified around the pathway structure or inputs have been highlighted, however alternatives have not been identified or modelled.

The company have submitted data and results for utilities and resulting cost effectiveness together with a probabilistic sensitivity analysis. The EAC have not examined these nor reported on them in this addendum.

This report has not been fact checked by the company, due to the time constraints in place.

Model structure

The model provided by the company is a decision tree, with an NHS perspective. The company state that there is a 2 month time horizon, based on available data. The end points of the decision tree are either improvement of symptoms or referral on to the next level of treatment until stage 3 is reached.

The comparator arm is standard care, and uses the model structure shown in figure 1 (derived from company model)

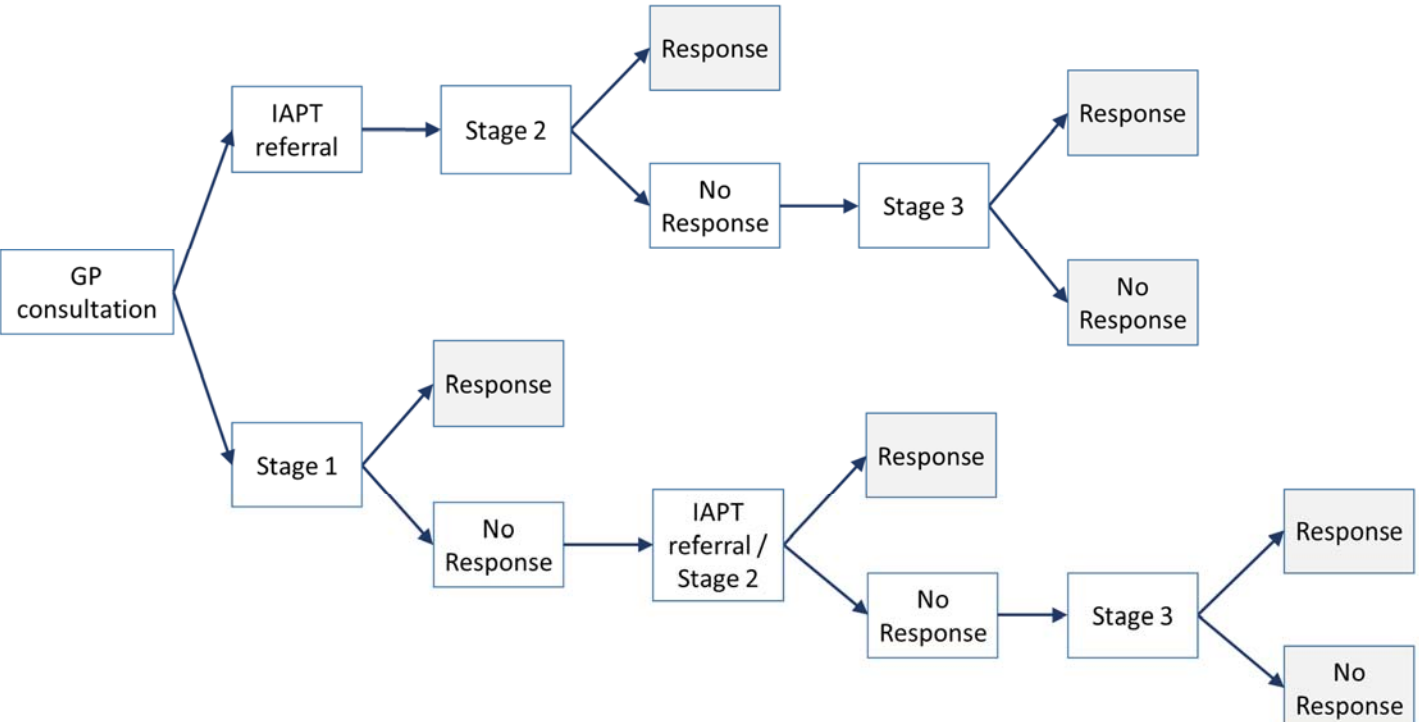

Figure 1 Standard care model

The stages in the model include the following treatments:

Stage 1 – GP led

Stage 2 – computerised CBT

Stage 3 – individual CBT, consisting of 8 sessions, each 60 minutes

The intervention arm of the model is shown in a simplified form in figure 2, where Alpha-Stim is provided prior to alternative interventions, and where standard care includes an identical structure to standard care in the comparator arm

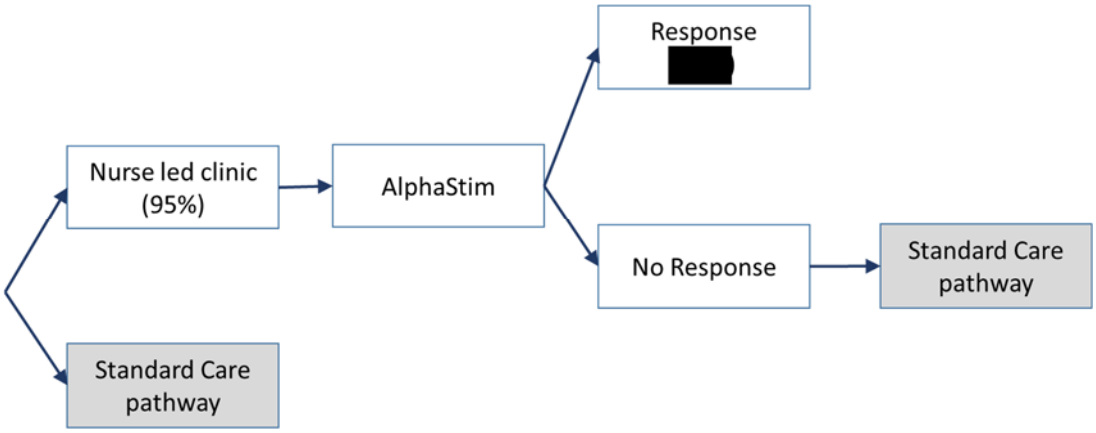

Figure 2 Intervention model, where Standard Care pathway is represented by figure 1

Table 2: Assumptions identified by Cedar, with their impact are:

• **Model assumption**	• **EAC Comment**
• AlphaStim is provided prior to any other treatments, and those who have a response do not require further treatment	• This removes patients from the standard care pathway at an early stage, making the model very resilient to sensitivity analysis if the assumptions are all correct. • In the Royal study (unpublished), patients had a choice of AlphaStim and other first line treatments, which may have been in addition to Alpha-Stim
• AlphaStim is not used concurrently with other treatments	• Linked to previous assumption. If it is provided concurrently cost savings will be reduced.
• There is a linear approach to treatment, with interventions occurring consecutively and remain in the described order (with increasing levels of cost / interaction).	• This is unlikely to reflect reality, with clinicians describing a more complex system. Where other assumptions hold true, and AlphaStim avoids entry to the standard care pathway, the actual structure of the standard care pathway is less important. If AlphaStim is provided concurrently then there will be a greater impact.
• There is only one nurse or GP contact per treatment step (other than the actual CBT sessions)	• The Royal study reported a mean of 1 contact per 14.3 days for patients receiving AlphaStim and 1 contact per 15.3 days for those in the comparator group.
• Medication use is not explicitly included in the model.	• The Royal study reported that medication prescriptions were similar for both the patients receiving AlphaStim and those in the comparator group. The author noted (EAC correspondence) that medication prescription may not be a good indicator of actual medication use.
• The data for the comparator arm is assumed to be equivalent to Stage 1, however it is not clear from the preliminary results if this reflects reality	• In reality patients had a mix of several different treatments that were available to both the intervention and comparator cohorts.
• Patients go straight to the nurse led clinic without going to the GP initially	• The addition of a GP appointment to the AlphaStim pathway causes only a small reduction in cost saving.

• Use of AlphaStim reduces the number of patients requiring stage 3 intervention	• This is the key driver of the cost saving.
• There are no additional costs incurred after stage 3 intervention	• The EAC have not investigated this, however seems plausible for the model given the short time horizon. In reality over a longer time period there are likely to be costs.
• Patients can travel all the way through to stage 3 in the stated 2 month time horizon	• 2 months is a nominal stated time horizon based on available data for AlphaStim response.

Clinical inputs

Data for Alpha-Stim are taken from the unpublished study described earlier. In this study, Alpha-Stim was available to all participants who consented to the study as were the other elements of the pathway: Self-help, talking therapies and medication.

Table 3: Summary of probabilities with EAC comments

Description	probability	Source	EAC comment
Presentation to Nurse-led practice	**0.95**	*Assumption*	Behaviour of the model to changes in this probability and AlphaStim success rate are presented as two way sensitivity table later in report.
Response to AlphaStim	[redacted]	*Study Outcomes*	Intervention data for Royal study (n=[redacted]). Patients were also offered additional therapies.
IAPT Referral	**0.25**	*Assumption*	These patients bypass stage 1 and go directly to stage 2. Stage 1 incurs no costs and results in some patients requiring no further treatment. Any patients that do not respond to stage 1 are then placed on the IAPT pathway. Therefore the actual number using IAPT is higher than this.
Response to Stage 1 (GP led)	[redacted]	*Study Outcomes*	Comparator data for Royal study. Treatment received by this group is a mixture of self-help, talking therapies and medication.
Response to Stage 2	**0.51**	*Andersson et al., 2019*	Meta-analysis, identifying patients with mood related disorders

(Computerised CBT)			
Response to Stage 3 (iCBT)	**0.54**	*Gyani, A. et al. 2013*	Data also used for initial submission for IAPT pathway

Costs

Table 4: Summary of costs with EAC comment

Description	**Cost**	***Source***	**EAC comment**
AlphaStim cost per Patient	**£ 70.00**	*Study Outcomes*	As per IAPT model
Cost of Individual CBT	**£ 1,359.78**	*Radhakrishnan et al, 2013*	The EAC used a cost of £921.29 for the IAPT pathway, based on data from the same source. This reduces the cost saving, but the model remains cost saving.
Cost of computerised CBT	**£ 65.87**	*McCrone et al., 2004*	This paper reports an overall cost increase of £40 per service user when using cCBT compared to standard care. The model uses inflation indices to increase cost to 2019. The cCBT intervention used in the paper was costed at £14.50 per session, with 8 sessions.
GP - led consultation (20 mins)	**£ 85.10**	*Study / Curtis & Burns, 2019*	Appropriate source
Nurse - led consultation	**£ 14.00**	*Study / Curtis & Burns, 2019*	Appropriate source

Costs for computerised CBT are taken from a study (McCrone et al 2004) that looked at all service cost before and after intervention with computerised CBT and found that costs were £40 higher per service user post intervention. The cost used is therefore not a direct cost of the intervention,

and is using a different approach to the other costs in the model which are based on the actual intervention costs, but do not take into account impacts on other areas of the service.

The computerised CBT intervention used in the study (McCrone et al 2004) was costed at £14.50 per session, with 8 sessions. Any increase in the cost of stage 2 intervention would increase modelled cost savings due to Alpha-Stim.

Results

Table 5: Summary of results for submitted base case

•	• **Control**	• **AlphaStim**	• **Cost saving**
• **Total cost per patient**	• £502	• £216	• **£285**

Figure 3 shows the distribution of the patients across the AlphaStim pathway, and the associated costs. Within the standard care pathway (in both arms of the model) the largest costs are for stage 3 interventions.

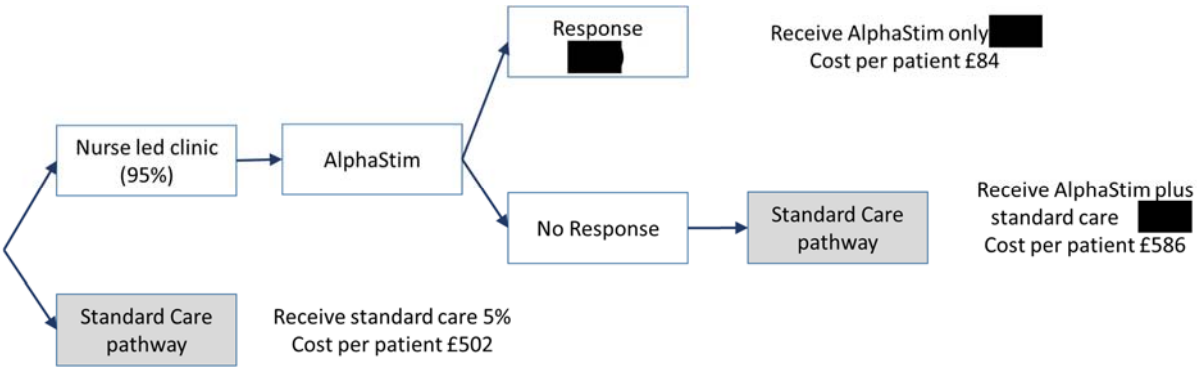

Figure 3 Intervention arm of model including costs per patient for main branches

Sensitivity analysis

Key drivers

A key driver is the number of patients requiring stage 3 treatment in each arm, as this is the most costly intervention included. This is influenced by the number of patients who receive and respond to Alpha Stim, and the success rate for stage 2 treatment. In the model many patients bypass stage 1 treatment, reducing the impact on the overall outcomes of the model.

Alpha Stim treatment cost per patient

The threshold cost of Alpha Stim per patient at which it is no longer cost saving (in the model as submitted) is approximately £370, as shown in figure 4.

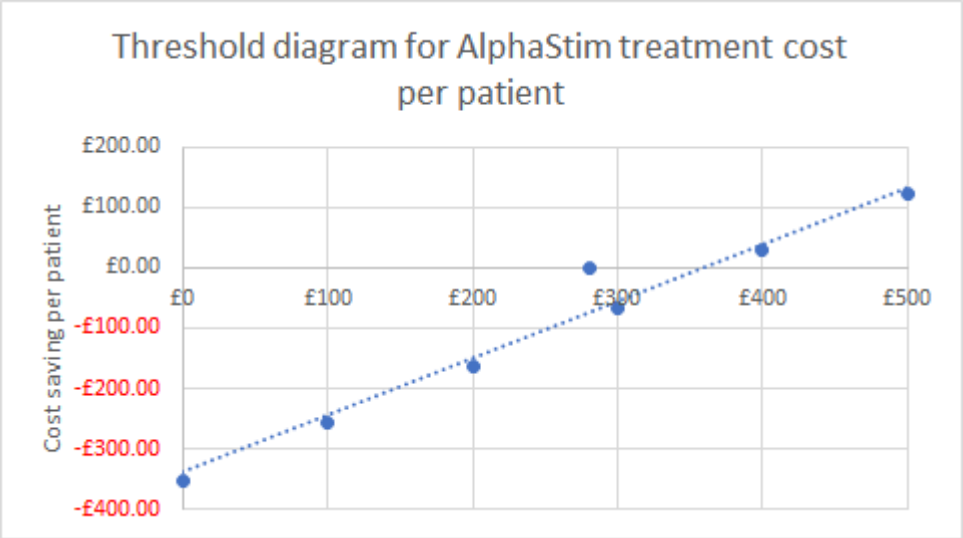

Figure 4 Threshold diagram for Alpha Stim device costs per patient

Alpha Stim responders

A two way sensitivity analysis for the probability of using a nurse led clinic and the probability of a response to Alpha Stim was used to consider the effect of changing the number of patients avoiding the standard care pathway (as illustrated in figure 3). As submitted, the model remains cost saving unless the probabilities are reduced to very low figures.

Table 6: Two way sensitivity analysis

Cost saving per patient (base case is £285)		Referral to nurse led practice (AlphaStim pathway)					
		0	**0.2**	**0.4**	**0.6**	**0.8**	**1.0**
Alpha Stim response	**0**	£0	-£17	-£34	-£50	-£67	-84
	0.2	£0	£3	£7	£10	£13	£16
	0.4	£0	£23	£47	£70	£93	£117
	0.6	£0	£43	£87	£130	£174	£217
	0.8	£0	£63	£127	£190	£254	£317
	1	£0	£84	£167	£251	£334	£418

Where there are no referrals to the nurse led practice, the intervention arm is effectively standard care and there is no cost difference between the two arms of the model.

Removal of stage 3 treatments

Within the stated 2 month time horizon, patients may be unlikely to escalate to Stage 3 interventions (iCBT). If stage 3 is removed from the model the cost saving is reduced to £9.40 per patient, as fewer costs are avoided over that time period. Ideally the model would have a much longer time horizon and an NHS and personal social services perspective would include all treatment stages in both primary care and the IAPT pathway and the use of medication. This would be difficult currently due to a lack of data for both Alpha Stim over extended time periods, and for the wider pathway.

Conclusions

The submitted model is cost saving and robust to most sensitivity analysis. The cost savings modelled are achieved mainly through avoiding escalation to more intensive, higher cost interventions.

The model does not capture the reality of treatments being offered in combination or in varying orders, and the varying use of medication. It also does not capture repeated visits to the GP or nurse. The clinical inputs are taken from a source with a much less clear and structured pathway than the model uses.

If Alpha Stim is provided in combination with other treatments, or if fewer patients are referred to more intensive interventions, then any cost saving will be reduced.

Other factors to consider would be the duration of effect from Alpha Stim, which is not currently known, and the likelihood that some patients would re-use Alpha Stim on several occasions over a number of years.

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Appendix: Stress testing model

Scenario	Control (per 1000 patients)	AlphaStim (per 1000 patients)	Cost saving (per 1000 patients)	Notes
Base case	£501,806	£216,462	£285,344	
The number of patients equal to 0.	£0	£0	£0	Correct result when put into model parameters - can't change in summary
AlphaStim cost = £0	£501,806	£149,962	£351,844	cost of alpha stim lower - still a cost, due to additional treatments in pathway
AlphaStim cost = £1000	£501,806	£1,099,962	-£598,156	Becomes cost incurring as expected
Cost of all CBT =£ 0	£85,100	£102,976	-£17,876	Both branches reduce cost, as CBT in both, but control reduced by more, as expected
Cost of all iCBT=£5000	£1,517,002	£492,941	£1,024,061	Both branches increase cost, as CBT in both, but control increased by more, as expected
Nurse cost = 85.10	£501,806	£284,007	£217,799	Increase in AlphaStim, but still cost saving - not huge impact
Response rate for AlphStim = 0	£501,806	£581,606	-£79,800	If put in a user value in Model Parameters Cell D15, the no response value does not recalculate - only a problem if changing values. If change Cell

				F15, then get the answers recorded here.
Response rate for AlphStim =100%	£501,806	£104,890	£396,916	As above, for either option the impact is diluted by the number of other treatments in the pathway that remain unchanged.
Success rate of iCBT (stage 3)=0%	£501,806	£216,462	£285,344	Branches 3,10,14 = £0, but no impact on the actual model as there is no alternative treatment if non successful. Cost is dependent on the treatment not the outcome.
Success rate of cCBT (stage2) = 0%	£896,504	£323,954	£572,550	Both increase, as more patients go through to stage 3. But for control, all now reach stage 3. In AlphaStim 73% don't change
Success rate of stage1 = 0%	£817,257	£302,372	£514,885	Both increase, as more patients go through to stage 2 & 3. Less increase in cost saving than row above, as some patients bypass stage 1 in both arms
Success rate of iCBT (stage 3)=100%	£501,806	£216,462	£285,344	As before, no difference in total costs

Success rate of cCBT (stage2) = 100%	£122,587	£113,185	£9,402	Still cost saving, but a lot less. No patients going through to stage 3 now.
Success rate of stage1 = 100%	£268,139	£152,825	£115,314	As many patients bypass this stage, has a reduced impact