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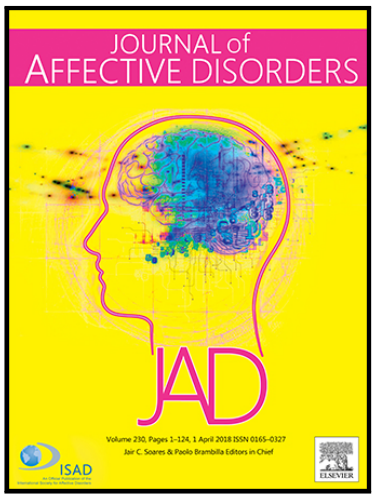

Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder.

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Highlights

- In treatment seeking patients with generalised anxiety disorders, cranioelectrostimulation is as effective against anxiety and depression symptoms, confirming previous meta-analysis of randomised controlled trials of volunteers with anxiety;
- Rates of remission of anxiety at 12 and 24 weeks are slightly lower than individual cognitive behaviour therapy;
- The clinical effects of 6-12 weeks daily CES are maintained for a further 12 weeks without using CES;
- Compared to individual cognitive behaviour therapy, alpha-stim CES is cheaper to use

Clinical effectiveness and cost minimisation model of Alpha-Stim cranial electrotherapy stimulation in treatment seeking patients with moderate to severe generalised anxiety disorder.

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Abstract

Background. Cranial electrotherapy stimulation (CES) is a well-tolerated neuromodulation treatment with demonstrated trial efficacy in anxiety disorders. The aim of the current study was to demonstrate its clinical and cost effectiveness during and after CES in people with generalised anxiety disorder (GAD) who had not responded to low intensity psychological treatment in a routine health service.

Methods. Consecutive sample of eligible patients with GAD waiting for individual cognitive behaviour therapy (CBT) selected from two publicly funded services in England. They received 60 minutes per day Alpha-Stim CES for 6-12 weeks. Primary outcome was remission on the GAD-7 scale at 12 and 24 weeks. Cost effectiveness was examined using a cost minimisation model of direct health costs.

Results. Of 161 patients recruited, 72 (44.7%) and 77 (47.8%) achieved remission on the GAD-7 at 12 and 24 weeks respectively with 122 (75.8%) receiving at least 6 weeks CES. Mean (sd) GAD-7 score at baseline significantly improved from 15.77 (3.21) to 8.92 (5.42) and 8.99 (6.18) at 12 and 24 weeks respectively ($p<0.001$). 80 (49.7%) participants required further individual CBT. CES provided a saving of £540.88 per patient (95% CI -£327.12, £648.69).

Limitations. Participants were not randomised and there was no control group. Only 48 (29.9%) participants completed every assessment.

Conclusion. In patients with generalised anxiety disorder not responding to low intensity psychological treatment, 6-12 weeks daily Alpha Stim CES may be effective after treatment and 3 months later, thereby reducing the need for individual CBT and saving health costs.

247 words

Keywords

Cranial electrotherapy; neuromodulation; generalised anxiety disorder; cost effectiveness.

Abbreviations

AIS - Athens Insomnia Scale; Alpha-Stim AID - cranial electrotherapy stimulator for control of anxiety, insomnia and depression; CBT - cognitive behaviour therapy; CE - Conformité Européene, European Union regulatory marking; CES - cranial electrotherapy stimulation; CI - confidence interval; CSRI - Client Service Receipt Questionnaire; DSM-IV- Diagnostic and Statistical Manual of Mental Disorders 4th Edition; EEG - electroencephalography; EQ5D-5L - Euroqol; FIML - full information maximum likelihood estimation; fMRI – functional magnetic resonance imaging; GAD - generalised anxiety disorder; GAD-7 – self-rated measure of generalised anxiety disorder symptoms; GLM - general linear model; HE – health economics; iCBT – individual cognitive behaviour therapy; IAPT - Improving Access to Psychological Treatment service; IRAS – Integrated Research Application Service; ITT - intention to treat; MCAR - missing completely at random; NHS - National Health Service; NICE - National Institute for Clinical Excellence; NRES – National Research Ethics Service; PHQ-9 - Personal Health Questionnaire 9 item; PSA - Probabilistic sensitivity analysis; PSSRU - Personal Social Services Research Unit; RCT - randomised controlled trial; RM ANOVA - repeat measures analysis of variance; WASA - Work and Social Adjustment Scale

Introduction

Generalised anxiety disorder (GAD) is a common and persistent mental disorder with a point or annual prevalence of 2.1 to 4.4% (Hunt et al, 2002; Grant et al, 2005; Remes et al, 2017; Ruscio et al, 2017). GAD is often present with other mental disorders such as depression, other anxiety disorders, insomnia and physical illness (Chapman et al 2010; Ruscio et al, 2017), all of which can lead to considerable health expenditure (Sandelin et al, 2013). According to the National Institute for Clinical Excellence (NICE) Guideline for Generalised Anxiety Disorder for England and Wales (NICE, 2011), the first step in the management of GAD is education about the condition and monitoring delivered in primary care. The second step is low intensity psychological intervention of the person's choice, which is provided by the Improving Access to Psychological Treatment service (IAPT) in all parts of the National Health Service in England (NICE, 2011), usually in the form of facilitated computerised cognitive behaviour therapy or bibliotherapy (Gyani et al, 2013). While these approaches are relatively cheap and effective, many people with GAD do not improve and require additional treatment (Andrews et al, 2018). The third step NICE recommended intervention is either a high intensity psychological intervention such as individual cognitive behaviour therapy (iCBT), also delivered by IAPT services and relatively expensive, or drug treatment, initially with selective serotonin reuptake inhibitor antidepressants but if these are ineffective then more expensive drugs such as pregabalin are used. There can be a substantial delay before iCBT can be offered (Sandelin et al, 2013).

Cranial electrotherapy stimulation (CES) was first utilised to induce sleep and relaxation using bursts of small electric currents applied to the head in the 1900s (Guleyupoglu et al, 2013). Improvements have taken place in electrode placement, use of battery driven devices and understanding of dose, frequency of treatment and waveform that is required to improve anxiety symptoms. Single courses of CES are associated with changes in electroencephalography (EEG) from delta (0-3.5Hz) and beta (12.5-30Hz) frequencies to more relaxing and alerting alpha frequencies (8-12 Hz) (Kennerly, 2004). Cortical and subcortical brain activation on fMRI have been demonstrated in people with high levels of anxiety (Feusner et al, 2012) and increases in plasma beta endorphins, adrenocorticotrophic hormone and cortisol (Liss and Liss, 1996; Shealy et al, 1998) after a single 20 minute CES treatment.

A recently published systematic review funded by the United States Department of Veteran Affairs identified five randomised controlled trials (RCTs) with 198 participants for anxiety disorders comparing active CES to sham CES (Shekelle et al, 2018). It concluded that there was low quality evidence of the effectiveness of CES for anxiety and depression symptoms in people with anxiety disorders at the end of treatment as well as evidence that CES does not cause serious side effects. A randomised controlled trial in 115 volunteers with a primary anxiety disorder showed the effectiveness of 5 weeks of active CES versus sham CES on anxiety and depression symptoms at the end of treatment (Barclay and Barclay, 2014). However, there have been no studies of the maintenance of clinical improvement or cost effectiveness of CES in treatment seeking patients with GAD who had not responded to second-line treatment as recommended by NICE (2011). Therefore we examined the clinical and cost effectiveness of 6-12 weeks CES treatment for treatment seeking patients with GAD who had not responded to facilitated computerised cognitive behaviour therapy or bibliotherapy over 24 weeks. These patients were all waiting for iCBT for GAD.

There are four aims to the current study to determine:

1. The proportion of patients treated with CES in IAPT services who reach the clinical threshold for remission (GAD-7 score of 7 or less; Spitzer et al, 2016), reliable improvement and recovery after treatment at 12 weeks.
2. The proportion of patients treated with CES in IAPT services who maintain the clinical threshold for remission (GAD-7 score of 7 or less), reliable improvement and recovery at 24 weeks.
3. If there are significant changes over 24 weeks in generalised anxiety, depression, insomnia, social adjustment and quality of life.
4. If the cost of CES offsets the cost of psychological treatment and other treatment over 24 weeks.

Method

Design. This is a study in routine care carried out after efficacy has been established against sham treatment in a meta-analysis of RCTs (Shekelle et al, 2018) to establish the effectiveness and costs in routine care settings as outlined by the United Kingdom Medical Research Council Complex Intervention Framework (2000) and the National Institute for Health and Care Excellence (2018). An open consecutive patient cohort design with 24 week follow up in National Health Service (NHS) mental health treatment settings in England was employed where all participants were offered Alpha-Stim cranial electrotherapy stimulation (CES) for 6-12 weeks if they had not reached remission with therapist or full guided self-help and were waiting to receive individual cognitive behaviour therapy (iCBT).

Setting. Two NHS Improving Access to Psychological Treatment (IAPT) services in the same county in England covering a more affluent urban and rural area and a less affluent inner city area. The services were run by two different NHS organisations. All data and treatment were delivered by staff who were independent of the company who makes Alpha Stim CES. Ethical approval for the study was granted by the Nottingham 2 NRES committee (IRAS206555).

Inclusion/exclusion criteria:

1. A score of 8 or more on GAD-7 scale, a 7-item self-rated measure of symptoms of generalised anxiety disorder (Spitzer et al, 2016), because nationally IAPT services determined that further treatment should be offered after full or guided computerised self-management or bibliotherapy if a person scores above the threshold for remission i.e. a total score of 8 or more.

2. A clinical diagnosis of generalised anxiety disorder alone or in combination with a comorbid depression or other anxiety disorder e.g. obsessive compulsive disorder or physical health morbidity. Excluded was a diagnosis of any other mental disorder e.g. substance use disorder, eating disorder, bipolar disorder, non-affective psychosis. In keeping with an implementation study the diagnostic information used for the inclusion and exclusion criteria were made on clinical grounds without using any standardised psychiatric interviews by clinically qualified mental health professionals independently of the research team.

3. On waiting list for individual CBT (high intensity psychological intervention).

4. Does not require urgent clinical care.

5. If female not known to be pregnant.

6. Implantation with a pace maker or an implantable cardioverter device (ICD) are exclusions.

6. Gives informed written and oral consent to the study.

7. Agrees to return Alpha-Stim equipment at the end of the study.

Being on medication did not lead to exclusion.

Outcome measures:
These are standard clinical outcome measure employed routinely by the NHS IAPT services with the addition of measures of insomnia, quality of life and an economic interview to assess health costs. They were collected face to face at baseline. Clinical outcome and quality of life measure were collected at four, six, eight, 12 and 24 weeks by e-mail, telephone or post according to participant preference. A second economic interview was conducted by telephone or Skype at six months according to participant preference. All participants who completed the economic interview were given a £10 gift voucher in recognition of the time given to completing the research outcome assessments.

Primary outcome measure:
The primary outcome is the proportion of participants who reach remission (7 points or less) at 12 and 24 weeks on the GAD-7 since IAPT services are paid according to the proportion of patients who reach this threshold after treatment in their service (Richards and Borglin, 2011). Other key outcomes are the proportion of cases who meet a clinically important ("reliable improvement") 5 point improvement on the GAD-7 at 12 and 24 weeks (Richards and Borglin, 2011), the proportion who meet criteria for recovery (GAD-7 score of 7 or less and also exhibiting a 5 point drop in GAD-7 score) at 12 and 24 weeks (Richards and Borglin, 2011), and the effect size of the change in GAD-7 score over 12-24 weeks. A clinically important deterioration is an increase in GAD-7 score of 5 points at 12 and 24 weeks (Richards and Borglin, 2011).

Secondary outcome measures:
1. Personal Health Questionnaire, 9-item (PHQ-9; Kroenke et al, 2001), a 9-item self-rated measure of the severity of depression symptoms. Remission is a total score of 9 or less at 12 or 24 weeks in those who had scored 10 or more at baseline, reliable improvement is a drop of 6 points or more, and recovery is a score of 9 or less and a 6 point drop at 12 and 24 weeks (Richards and Borglin, 2011). We also examined the effect size of the change in PHQ-9 score symptoms from baseline to 12 and 24 weeks.

2. Athens Insomnia Scale (AIS; Soldatos et al, 2000). This scale has 8 items with a maximum score of 24. A score of 6 indicates a possible sleep problem and 4 indicates recovery (Soldatos et al, 2003). Therefore remission is defined as the proportion of people who score a total of 4 or less at 12 and 24 weeks. No data exists on reliable improvement so a drop of 50% in baseline score by 12 and 24 weeks was used. Recovery is the proportion of people who showed a drop of 50% in baseline score and scored 4 or less at 12 and 24 weeks. We also examined the effect size of the change in insomnia symptoms from baseline to 12 and 24 weeks.

3. Work and Social Adjustment Scale (WASA; Mundt et al, 2002), an 8-item self-rated measure of work and social function. A total score of 20 or more indicates considerable impairment in function (Mundt et al, 2002). A return to normal function requires a total score of 10 or less and functional recovery requires a total score of 11 or more at baseline with a drop to 10 points or below by 12 and 24 weeks (Mundt et al, 2002). We also examined the effect size of the change in WASA score from baseline to 12 and 24 weeks.

4. EQ5D-5L (EuroQol, van Hout et al, 2012), a 6- item self-rated measure of health utility and quality of life. We examined the effect size of the change in EQ5D-5L from baseline to 12 and 24 weeks.

Economic interview:

We used the Client Service Receipt Interview (CSRI; Beecham and Knapp, 1992) adapted for use in studies of anxiety disorders in primary care and community settings. It was completed at baseline and 24 weeks.

Procedure.

Consecutive treatment seeking patients who received low intensity IAPT interventions (therapist guided self-management on a computerised CBT programme or bibliotherapy for GAD) but had not reached a total score of 8 or more, were unlikely to meet any exclusion criteria for the study, and were willing to be placed on a waiting list for iCBT, were identified from IAPT service records. IAPT staff contacted a potential participant to seek permission for their contact details to be passed to the study team who checked their eligibility over the phone. A face to face meeting was arranged with a member of the study team who checked the inclusion/exclusion criteria and sought written informed consent. If the participant consented study staff showed the participants how to use the Alpha-Stim CES device, outlined how to obtain support while using it, and negotiated the return of the CES device at the end of 6-12 weeks treatment. Women of child-bearing potential completed a urine pregnancy dipstick human chorionic gonadotropin test.

Alpha-Stim AID is a CE marked medical device which is marketed for the alleviation of psychological conditions including anxiety, insomnia and depression, through using cranial electrotherapy stimulations (CES) which are tiny electric currents applied through ear clips worn for 60 minutes per day. The treatment provided by the device is therefore non-invasive, non-pharmacological, and can be used as adjunctive treatment to drug or psychological treatment or a treatment on its own. All participants were offered 60 minutes per day of alpha-stim CES treatment at a current of one hundred micro amps per day 7 days per week for 6 consecutive weeks. The 60 minutes session starts when the ear clips are attached and stops automatically when the hour is finished. The device was not locked because it would not be in usual clinical practice. The device did not automatically record adherence to treatment. Participants could choose to continue with the same CES treatment for a further 6 weeks, thereby completing 12 weeks CES treatment in total. At the end of 12 weeks the participants could not receive any further CES treatment. Since this was a naturalistic study, decisions concerning if and when iCBT might be received by the participant were made by IAPT staff with the participants; the study team did not influence this decision. If participants started iCBT during the 6-12 weeks of CES, they could continue with CES while receiving iCBT at the same time. Similarly general practitioners could independently decide to place the patient on medication for

GAD at the same time as participants continued to receive CES. A summary of the procedures of the study is shown in Table 1; as well as outcome measures, adherence to CES and side-effects were recorded at each study visit.

Sample size.

A meta-analysis of 5 CES RCTs estimates an effect size of at least 0.60 (Shekelle et al, 2018). On this basis remission might be expected in 26.5% patients with GAD receiving alpha stim CES in IAPT settings. The aim was to recruit a sample with at least 25 participants achieving remission after alpha stim CES at 12 weeks and followed up at 24 weeks; a sample of 160 would be required assuming 40% loss to follow up by 24 weeks.

Statistical analyses.

Prior to statistical analyses, data screening was conducted to evaluate the tenability of assumptions specific to the general linear model (GLM). These assumptions included normally distributed outcome variables, independence of observations for different subjects, and homogeneity of covariance matrices within subjects across repeated measurements. The assumptions of the GLM were tenable except for homogeneity of covariance within subjects on their measurements over time. The Greenhouse-Geiser adjustment was applied to *F*-statistics and degrees of freedom when violations appeared. After data screening, analyses proceeded using a within-subjects repeated measures analysis of variance (RM ANOVA) for the primary outcome and secondary outcome variables. Additionally, regarding aims 1 and 2, descriptive analyses were conducted to determine remission, reliably improvement and recovery.

To answer our research aim 3, we used a within-subjects univariate repeated measures analysis of variance (RM ANOVA). Separate univariate RM ANOVAs were conducted for each outcome variable in two distinct phases. The first set of analyses proceeded using data from the empirical sample. The second set of RM ANOVA analyses included an intention-to-treat (ITT) analysis strategy using a full complement of scores on each outcome variable. The following section includes information specific to the ITT analytic approach.

Intention-to-treat (ITT) analysis avoids overoptimistic estimates of the efficiency of an intervention resulting from the removal of non-compliers by accepting that noncompliance and protocol deviations are likely to occur in clinical practice. Intention-to-treat analyses was applied including all patients as they were assigned at baseline, regardless of their adherence to treatment, the treatment they received or any subsequent withdrawal from the study (Fisher, 1990). To evaluate the type or pattern of missing scores for each outcome measure, the missing completely at random (MCAR) test was employed (Little and Rubin, 2002; Enders, 2010). Once the data was determined to adhere to MCAR (i.e. p >.05), replacement of scores proceeded using model-based full information maximum likelihood (.FIML) estimation.

Health economics

In order to determine the cost impact of introducing CES into the pathway as a second-line treatment instead of or prior to individual CBT (iCBT), a cost minimisation analysis was undertaken using a health economic (HE) model decision tree (see Figure 1). In both branches of the HE model the patient population was non-responders to low-intensity guided or full computerised self-help or bibliotherapy given as the first-line treatment. The decision tree was populated with the

probabilities of response to second line CES treatment from the study versus second-line iCBT with the remission rate of 54.2% from Gyani et al (2013) which is the average remission rate between guided and full self-help groups in that study. In addition, the same probability of outcome from subsequent iCBT sessions given to non-responders in both arms was modelled as in the current pathway (treatment as usual) such that for non-responders to second-line iCBT a further course of the same number of iCBT sessions would follow. For non-responders to second-line CES up to two further courses of iCBT were included in the decision tree. In all cases successful response was measured by the achievement of the GAD-7 threshold of remission as used in the IAPT programme (Richards and Borglin, 2011). Neither a cost-utility analysis nor a cost-consequences analysis was employed because the study did not have a comparator for outcomes although EQ-5D results are reported here separately for Alpha-stim CES treatment.

The hypothesis tested in the HE model was that adding CES as a second-line treatment in the pathway will eliminate, for the proportion of patients who respond to CES, the need for the more expensive iCBT leading to cost savings. Although not included in the model, it would also potentially reduce waiting times for those patients who would still progress to iCBT since early response to available CES therapy promises to free up therapist resource for iCBT as well as potentially the number of iCBT sessions each participant would need after receiving CES. The HE model used a 6-month time horizon, reflecting the expected duration of GAD response (NICE, 2011) and including the time period for consecutive treatments of CES and/or iCBT. Given this short time horizon, costs were not discounted.

The modelling was undertaken from the United Kingdom NHS payer perspective with prices uplifted using the most recent national annually published resource, the PSSRU Unit Costs of Health and Social Care 2017 (Curtis and Burns, 2017) which gave compounded ratios for an uplift up to 2016.

Costs were derived for CBT from Radhakrishnan et al (2013) for 60 or 90 minutes of iCBT (£98.59 or £ 176.97 per session) uplifted from 2010 to 2016 prices using the appropriate ratio of 1.09 yielding £ £110.96 and £199.17 respectively. Overall treatment costs were computed for 8 sessions of 60 minutes iCBT, as in the 'standard of care' model, yielding a total cost of £887.68. For comparison, the model was also constructed with alternative choices of two additional more expensive iCBT regimes: the 'Clark and Wells model' with 14 sessions of 90 minutes sessions of iCBT, costing £2788.43 in total and the 'Heimberg model' with one session of 90 minute iCBT followed by 15 sessions of 60 minutes iCBT, costing £1863.57 in total (NICE, 2013).

Alpha-stim CES cost per treatment was a manufacturer estimate from the unit cost of the device of £450.00 (excluding valued added tax) with a utilisation of 15 patients over an average product lifetime of 3 years (based on a 10 week sole use per patient). It allowed for losses with respect to the quoted 5 year warranty that was estimated to reduce average product lifetime by 2 years. A Additional therapist time, postage and consumables was estimated at £40, yielding £70 per treatment.

A probabilistic sensitivity analysis (PSA) was undertaken on cost of treatment, probability of response and utilisation of response with parameters as shown in Table 2 (York Health Economics Consortium, 2016). In addition a one-way deterministic threshold analysis was performed on cost to find the price at which the intervention would no longer be cost saving. Probabilistic sensitivity analysis (PSA) is a technique used in economic modelling that allows the quantification of the level of

confidence in the output parameters of the analysis, in relation to the uncertainty in the model inputs. In the probabilistic analysis, the parameters' value from clinical trials, observational studies or in some cases expert opinion are represented as distributions around their deterministic value. A set of input parameter values is drawn by random sampling from each distribution, and the model generates outputs (cost and health outcome), which are stored. This is repeated in many iterations of the model (typically 1,000 to 10,000), resulting in a distribution of outputs that can be graphed on the cost-effectiveness plane, and analysed.

Results

Figure 2 shows the flow of participants through the study. Only 22% of potentially eligible patients agreed to take in the study. All 161 participants started CES treatment and 112 (69.6%) completed at least 6 weeks treatment. Of the 49 (30.4%) participants who withdrew from treatment by 12 weeks, nine (5.6%) could not find the time to complete the treatment, four (2.5%) withdrew because of no improvement, four (2.5%) withdrew because of side effects (two with headaches and insomnia, one with nausea and one with a strange feeling after use), two (1.2%) withdrew because they felt better, and 30 (18.6%) gave no reason. Of the 161 participants, 80 (49.7%) had iCBT. Eighty-one (50.3%) completed follow ups to 12 weeks and 72 (44.7%) to 24 weeks.

Table 2 shows that participants were drawn from a broad range of ages and nearly three quarters were female. The overwhelming majority were white British, most had at least high school education, married and were in employment. However, the mean baseline scores were in the severe range for GAD (Spitzer et al, 2001), moderately severe range for depression (Kroenke et al, 1999), showed significant sleep difficulties (Soldatos et al, 2004), substantial functional impairment (Mundt et al, 2002), and low health utility comparable to scores for out-patients with a broad range of physical and mental disorders (van Hout et al, 2012).

Table 3 shows the primary outcome. By 12 weeks, 72 (44.7%) participants achieved remission and recovery on the GAD-7 at 12 weeks and 76 (47.2%) at 24 weeks. The proportions of participants achieving reliable improvement on the GAD-7 were 102 (63.4%) and 105 (65.2%) at 12 and 24 weeks respectively. No patient showed reliable deterioration at 12 or 24 weeks. There was a drop in GAD-7 score from mean (sd) 15.77 (3.21) to 8.92 (5.42) by 12 weeks and this is maintained to 8.99 (6.18) at 24 weeks, a mild degree of GAD-7 symptoms by 12 and 24 weeks. The within-subjects effects is statistically significant ($F=72.02$, $df1=3.7/df2=563.74$, $p<0.001$) and the effect size is medium (partial eta square=0.31). The vast majority of the drop in GAD-7 is experienced in the first 6 weeks and there is no statistically significant difference between week 6 and any subsequent time point up to week 24. The same pattern is seen in 48 participants with assessments at every time point except the effect size of the within subjects treatment effect was large rather than medium (Appendix Table 1). Of the 81 participants who only received CES, 49 (60.3%) achieved remission on the GAD-7 at 12 weeks and 53 (65.4%) achieved remission on the GAD-7 at 24 weeks. Of the 25 participants who received both CES and iCBT, 17 (68%) achieved remission and recovery on the GAD-7 and 23 (92%) achieved reliable improvement at 12 and 24 weeks.

Table 3 shows that the effects on the PHQ-9 were similar in relation to the GAD-7 although a lower proportion achieved a reliable improvement at 12 and 24 weeks. The within subjects effect was significant ($F=42.89$, $df1=3.9/df=559.01$, $p<0.001$) with the mean PHQ-9 score dropping from the

moderately severe range to the mild range but the effect size was small (partial Eta square=0.21). There was some worsening of depression symptoms by week 24 and the fall in PHQ-9 score was only significant between baseline and 12 weeks but not 24 weeks. Only around a quarter of participants achieved remission on the Athens Insomnia Scale at 12 and 24 weeks. There was a statistically significant within-subjects drop in insomnia over the 24 period (F=42.69, df1=5.0/df=542.9, p<0.001) and the effect size was medium (partial Eta square=0.21).

Table 3 also demonstrates that just over a quarter of participants made a functional recovery on the WASA at 12 and 24 weeks with CES. Figure 2 and Table 3 show that there is a significant within-subjects effect of Alpha-Stim CES over the 24 weeks (F=17.35, df1=3.5/df=557.45, p<0.001) but the effect size is small (partial Eta square=0.10). The effects of Alpha-Stim CES on the EQ-5D-5L were very similar to the WASA with a significant within subjects effect over 24 weeks (F=13.94, df1=4.1/df2=651.3, p<0.0001) but the effect size is also small (partial Eta square=0.08).

The results of the health economics decision tree model populated with the costs and probabilities for the 8 session standard care model of CBT yielded the results as shown in Table 4. The costs and responses are presented for a cohort of 1000 patients. CES provided a saving of -£540,878 (95% CI [-£648,692, -£327,117]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CI [141.03, 227.82]). Using the "Clark and Wells model" of iCBT as comparator, CES provided a saving of -£1,637,410 (95% CIs -£1,914,463, -£1,175,437]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CIs [141.58, 226.12]). With the Heimberg Model as a comparator, CES provided a saving of -£1,212,463 (95% CIs -£1,429,369, -£843,394]) and the number of responses to treatment were increased by 187.56 per 1000 (95% CIs [140.79., 227.71]). Cost-outcome scatterplots for each model are shown in the Appendix.

Discussion

This study shows that in moderate to severe treatment seeking patients with GAD, nearly 45 per cent of patients achieved remission and 63 per cent reliable improvement in their self-rated anxiety symptoms with Alpha-Stim CES treatment. These improvements were maintained for a further 12 weeks after CES was completed whether or not patients received iCBT in addition. Most of the improvement with CES was seen in the first 4 weeks. It had a moderate effect size. Remission rates are lower than reported for iCBT in routine IAPT services in the UK (Radhakrishnan et al, 2013); however our sample had substantially higher scores than routinely reported for IAPT services (Radhakrishnan et al, 2013; NHS Digital, 2018). . Approximately 50 per cent of patients on the waiting list for iCBT received iCBT, thereby enabling the NHS IAPT services to treat other patients on the waiting list for iCBT. The mean severity of GAD-7 symptoms decreased from severe to mild and below case threshold over 12 weeks and remained at that level for 24 weeks. There were similar drops in depression symptoms and insomnia symptoms as well as improvements in function and quality of life although all of these effects were smaller with some slippage between 12 and 24 weeks. Although there was a significant drop in depression symptoms between baseline and 12 weeks, it was not significant at 24 weeks indicating that the effects of CES on depression symptoms had started to wane by 24 weeks. Overall a quarter of patients receiving CES regained a functional recovery. Alpha-Stim CES was well tolerated with only six (4%) patients stopping it because of side-effects and four (3%) because they were not making any progress. Compared to a standard course of

iCBT (eight sessions or longer), Alpha-stim CES reduced costs of care by £540 or more per patient and it was also cost effective.

The strengths of the study were that clinical and cost effectiveness was examined in a consecutive large sample of treatment seeking patients in universally available publicly funded services provided by the state irrespective of the ability to pay or health insurance. Inclusion criteria were set to reflect the criteria used by IAPT services to offer individual CBT. This criteria was set at 8 or more on the GAD-7 reflecting the upper end of mild severity compared to the usual clinical thresholds for mild , moderate and severe anxiety of 5, 10 and 15 on the GAD-7 (Spitzer et al, 2006). However 95 per cent of the sample had moderate or severe symptoms of GAD at baseline, well above the minimum threshold for entry to the study and the national NHS IAPT criteria for remission. They had already failed to improve with facilitated bibliography or computerised psychological treatment for GAD, so spontaneous improvement was unlikely. Placebo responses are less frequent in research participants with less severe anxiety or depression and in those who have not responded to previous active treatment for their condition (Stein et al, 2006; Weimer et al, 2015). Therefore the study shows the effectiveness of CES in a clinical treatment seeking sample of patients with moderate to severe treatment resistant generalised anxiety disorder.

There are important limitations of the study. There was no control group and the study was not a randomised controlled trial. However meta-analysis of previous RCTs of active CES versus sham CES already provides evidence that CES is effective in treating anxiety and depression symptoms (Shekelle et al, 2018). The United Kingdom Medical Research Council (2000) and National Institute for Health and Care Excellence (2018) recommend that implementation studies are completed in routine treatment settings to check that the efficacy seen in RCTs is translated into routine clinical practice settings. This study was therefore designed to meet this requirement, to examine if effectiveness is maintained after CES treatment completion, and if there were any cost savings from CES treatment. Such studies do not necessarily utilise control groups; they must enrol treatment seeking patients studied under routine care delivery. Alpha-Stim CES was more effective at achieving remission than we expected from the effect size in a meta-analysis of RCTs (Shekelle et al, 2018) with 44.7% patients achieving remission, comparable to iCBT in routine treatment settings, rather than 26.5% patients as we had planned.

The sample recruited only 22 per cent of those eligible to take part in the study. However, the offer to take part in this research and to receive this treatment came through cold calling by the clinical team through letter, e-mail or telephone call. If participants were prepared for the possibility of receiving CES by the IAPT services then uptake of CES might be higher. A strength of cold calling and lack of research team contact is that placebo responses to CES may have been low because of infrequent contact of the research team so that the effectiveness of CES in the study was not inflated compared to clinical practice.

Another limitation of the study was that the sample lacked ethnic diversity. The sample was drawn from all ages although there were greater proportions of younger and middle aged participants in the study, reflecting the composition of age groups in routine IAPT NHS services. As expected the vast majority of patients with GAD were female. There was a broad representation of education, marital status and employment status reflecting the age composition of the sample.

There was a high degree of attrition of the study to follow up with the loss of 55.2% by 24 weeks despite financial incentive to provide data as opposed to 40% that we had anticipated. The study was adequately powered because CES was more effective than we had expected. The results are similar between the ITT sample with imputed results and those completing all follow up assessments suggesting that the conclusions drawn from the whole sample using imputation are probably safe to make. We also only have a limited amount of information on the reasons that participants withdrew from CES or follow up. The most common reason given for withdrawal from CES is not being able to find the time to use CES for 60 minutes per day. The CES device was also not locked so some participants may have used a higher current than we instructed them to and got adverse effects that they chose not to report. We have no evidence that anyone did this. Almost as many dropped out of CES because it had worked as those who stopped because it did not. A limitation of the health economics analysis is that we did not consider the possibility that CES might have reduced the delay in receiving iCBT by freeing up capacity in other CBT therapists or that those patients who received both CES and iCBT might have had fewer iCBT sessions. Therefore cost savings from CES may be underestimated in treatment settings offering iCBT for GAD.

We did not personalise CES to each individual. It is possible that different waveforms of current, stimulus intensity and stimulation location might have been more efficacious for some participants (Guleyupoglu et al, 2013). Some participants may have tolerated 5 days of treatment with CES per week better than 7 days per week with higher completion rates of 6-12 weeks CES treatment.

As well as improvements in anxiety, there were improvements in depression and insomnia, two other potential indications for CES. Although the results are encouraging, further research is needed in patients with primary depression and primary insomnia disorders. There were also high remission, recovery and reliable improvement rates in GAD-7 score when participants received both iCBT and CES in the first 12 weeks. Research might explore if higher and more sustained rates of remission are in generalised anxiety disorder in trials of iCBT plus active CES versus iCBT plus sham CES.

In conclusion, we provide evidence that CES may be clinically effective and cost reducing during administration and for three months afterwards in routine treatment settings offering psychological treatments for moderate to severe GAD. CES improves the efficiency of these services, a critical issue because of the shortage and high turnover of psychological treatment staff, allowing them to reach their targets for remission with fewer highly skilled staff. As a result, it is also cost saving to such services even when a range of different assumptions are made about the delivery of psychological treatment.

5,268 words

Contributors:
All authors wrote the paper and commented on its final draft. RM and MC designed, sought funding, supervised data collection and interpreted the results of the study. LP designed, conducted and interpreted the analysis of the statistical results of the study. GX and RF designed, analysed and interpreted the analysis of the health economics of the study.

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Conflict of interest

The chief investigator (RM) and MC report no financial or other conflicts of interest for their involvement in the study. Part of LP's funding is from Electromedical Products International as a statistical consultant. RF and GX's institution received a payment for conducting the health economics analysis reported here.

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Table 1. Procedure and assessments in the study (n=161)

ASSESSMENT	VISIT 1 BASELINE	VISIT 2 WEEK 4	VISIT 3 WEEK 6	VISIT 4 WEEK 8	VISIT 5 WEEK 12	VISIT 6 WEEK 24
CONSENT	X					
TRAINING TO USE CES	X					
PREGNANCY TEST	X (*)					
GAD-7	X	X	X	X	X	X
EQ-5D-5L	X	X	X	X	X	X
CSRI	X				X	X
WASA	X	X	X	X	X	X
PHQ-9	X	X	X	X	X	X
AIS	X	X	X	X	X	X
ALPHA-STIM CES	Ongoing	Ongoing	Ongoing (**)	Ongoing (**)	Ongoing (**)	
ADHERENCE		X	X	X (**)	X (**)	
ADVERSE EVENTS		X	X	X (**)	X (**)	

(*) If a female of child-bearing potential

(**) If continuing with Alpha-Stim AID CES treatment between week 6 – week 12.

Figure 1. Decision Tree model for comparison of Alpha-stim CES pathway with individual cognitive behaviour therapy (iCBT) treatment as usual.

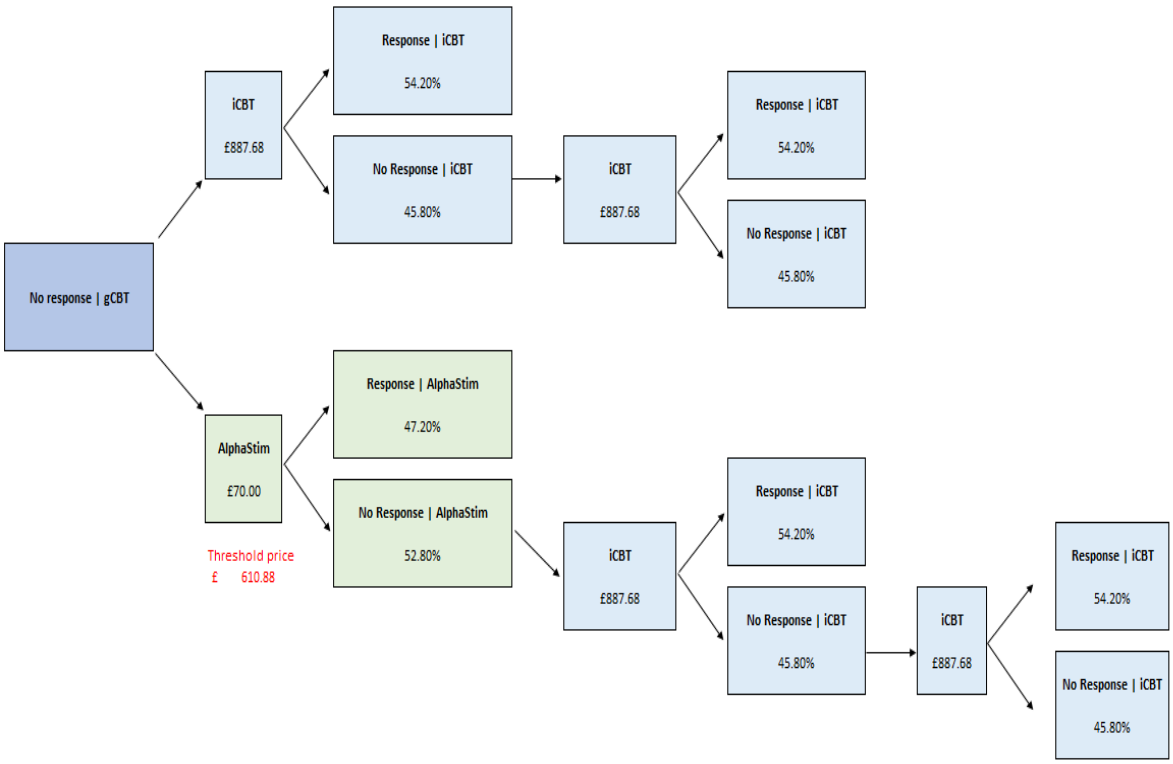

Figure 2: Flow into Study

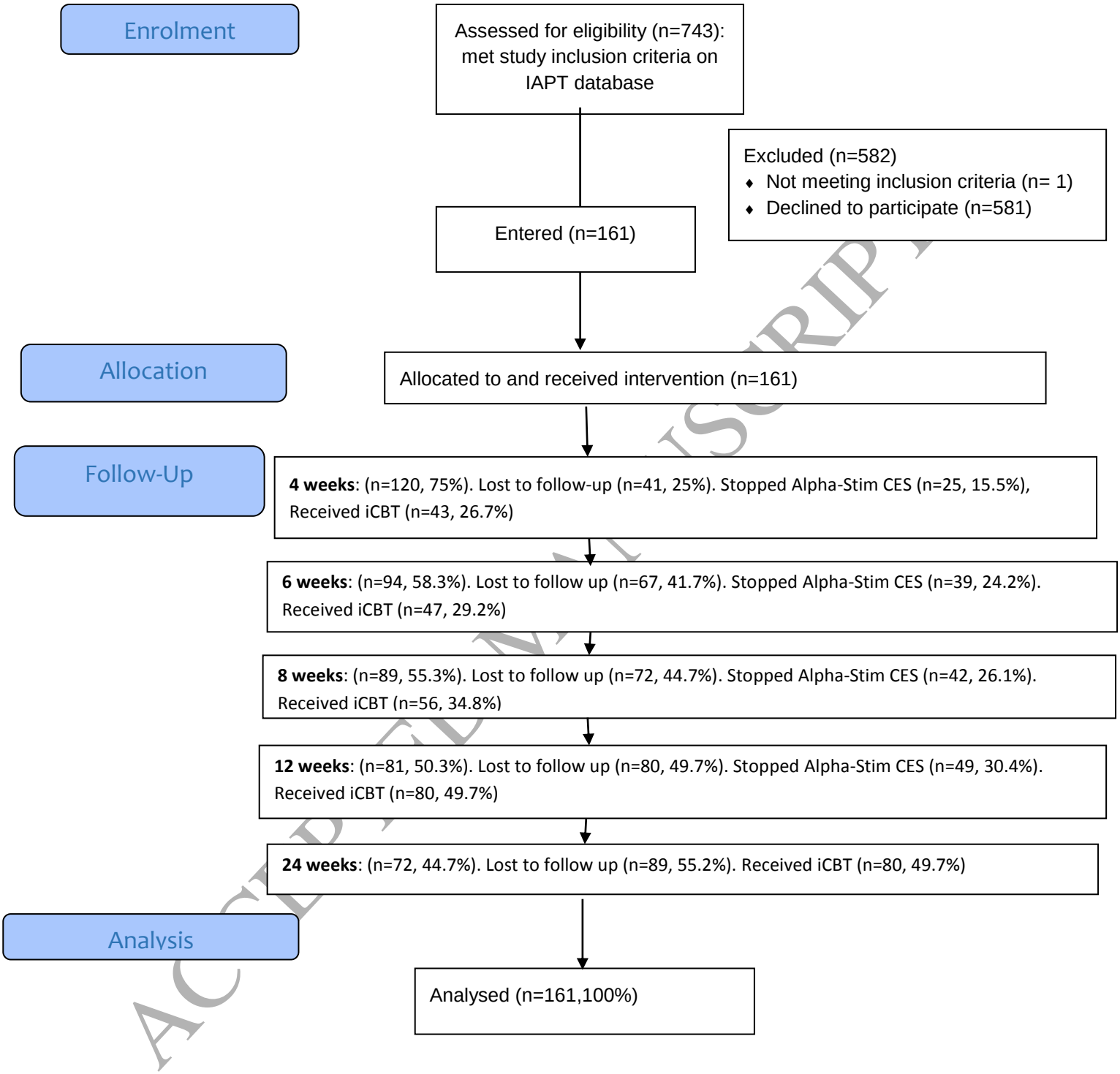

Table 2. Baseline characteristics of participants (n=161).

Variable	**Mean (sd) or n(%)**
Age, years	38.00 (14.2) (min=18, max=76)
Gender, female	118 (73.3%)
Ethnicity, white British	153 (95.0%)
Marital status: Married or cohabiting	95 (59.0%)
Single	50 (31.1%)
Divorced	12 (7.5%)
Widowed	4 (2.5%)
Education: No qualifications	5 (3.1%)
GCSE (left school at 16 years)	39 (24.2%)
A level or other non-degree higher qualification	67 (41.6%)
Degree	50 (31.1%)
Employment: Employed	106 (65.8%)
Unemployed	33 (20.5%)
Retired	11 (6.8%)
Student	7 (4.3%)
Homemaker	4 (2.5%)
GAD-7	15.77 (3.21)
PHQ-9	16.07 (4.94)
Athens Insomnia Scale	12.91 (4.82)
WASA	20.81 (7.74)
EQ-5D-5L	51.61 (19.0)

Table 3: Intention to treat analysis of remission, reliable improvement, recovery and mean (sd) continuous outcomes with Alpha-stim CES at 12 and 24 weeks (n=161).

Outcome	Remission 12 weeks n (%)	Reliable improve 12 weeks n (%)	Recovery 12 weeks n (%)	Remission 24 weeks n (%)	Reliable improve 24 weeks n (%)	Recovery 24 weeks n (%)
GAD-7						
Overall, n=161	72 (44.7)	102 (63.4)	72 (44.7)	77 (47.8)	105 (65.2)	77 (47.8)
No CBT, n=81	49 (60.5)	67 (82.7)	49 (60.5)	53 (65.4)	70 (86.4)	53 (65.4)
PHQ-9						
Overall, n=161	73 (45.3)	76 (47.2)	61 (37.9)	82 (50.9)	80 (49.7)	67 (41.6)
GAD-7 and PHQ-9						
Overall, n=161	62 (38.5)	75 (46.6)	54 (37.5)	69 (42.9)	75 (46.6)	59 (36.5)
AIS						
Overall, n=161	39 (24.2)	53 (32.9)	37 (23.0)	45 (28.0)	60 (37.3)	43 (26.7)
	Normal Function 12 weeks n (%)	**Functional recovery 12 weeks n (%)**		**Normal Function 24 weeks n (%)**	**Functional recovery 24 weeks n (%)**	
WASA						
Overall, n=161	28 (17.4)	43 (26.7)		29 (18.0)	48 (29.8	

Outcome	Baseline	4 weeks	6 weeks	8 weeks	12 weeks	24 weeks
GAD-7[1]	15.77 (3.21)	10.14 (4.86)	9.73 (4.89)	9.34 (4.58)	8.92 (5.42)	8.99 (6.18)
PHQ-9[2]	16.07 (4.94)	11.22 (6.09)	10.38 (5.91)	10.04 (6.46)	8.91 (5.78)	10.42 (6.97)
AIS[3]	12.91 (4.82)	10.27 (5.27)	10.18 (5.20)	9.72 (5.16)	8.81 (4.86)	7.94 (4.62)
WSAS[4]	20.81 (7.74)	18.27 (8.89)	16.95 (9.56)	15.94 (9.22)	14.89 (9.99)	15.98 (9.18)
EQ-5D-5L[5]	51.61 (19.00)	57.90 (20.15)	61.00 (20.47)	62.99 (21.08)	64.80 (21.72)	62.50 (22.97)

[1] Effect of treatment over time significant F =88.12, df1=5.0/df2=156.0, p < .001, partial Eta square = 0.74 (large); within subjects effect over time significant F=72.02, df1=3.7/df2=563.74, p < .001, partial Eta square = 0.31 (medium)

[2] Effect of treatment over time significant F=28.38, df1=5.0/df2=156.0, p < .001, partial Eta square = 0.48 (medium); within subjects effect over time significant F=42.89, df1=3.9/df=559.01, p < .001, partial Eta square = 0.21 (small)

[3] Effect of treatment over time significant F=40.85, df1=5.0/df2=156.0, p < .001, partial Eta square = 0.57 (large); within subjects effect over time significant F=42.69, df1=3.8/df=542.9, p < .001, partial Eta square = 0.21 (medium)

[4] Effect of treatment over time significant F=17.18, df1=5.0/df2=156.0, p < .001, partial Eta square = 0.36 (medium); within subjects effect over time significant F=17.35, df1=3.5/df=557.45, p < .001, partial Eta square = 0.10 (small)

[5] Effect of treatment over time not significant F=16.11, df1=5.0/df2=156.0, p < .001, partial Eta square = 0.34 (medium); within subjects effect over time significant F=13.94, df1=4.1/df2=651.3, p < .001, partial Eta square = 0.08 (small)

Table 4: Costs and responses of Alpha-Stim CES in relation to the eight session standard care model of CBT

	Deterministic	Probabilistic	Distribution	*Alpha*	*Beta*	*N int*	*N control*
Cost of Individual CBT	£887.68	£923.64	Gamma	*£ 887.68*	*1*		
Probability of Response to Individual CBT	54.2%	56%	Beta	*199.46*	*168.54*	*368*	*679*
Patients per Alpha-Stim CES lifetime	5.00	5.41	Gamma	*5*	*1*		
Per patient cost of Alpha-Stim CES	£70.00	£64.75	Calculated				
Probability of Response to Alpha-Stim CES	47%	39%	Beta	*45*	*55*		

	Expected Cost	**Lower 95% CI**	**Upper 95% CI**	**Expected Responses**	**Lower 95% CI**	**Upper 95% CI**
iCBT only	£1,294,233	£1,198,677	£1,392,923	701.68	650.29	751.85
AlphaStim	£753,355	£651,653	£981,087	889.24	860.29	907.14
Net	**-£540,878**	**-£648,692**	**-£327,117**	**187.56**	**141.03**	**227.82**

Appendix

Figure 1. Cost outcome scatterplot Alpha-Stim CES versus 8 session standard care model of iCBT (n=1,000 patients).

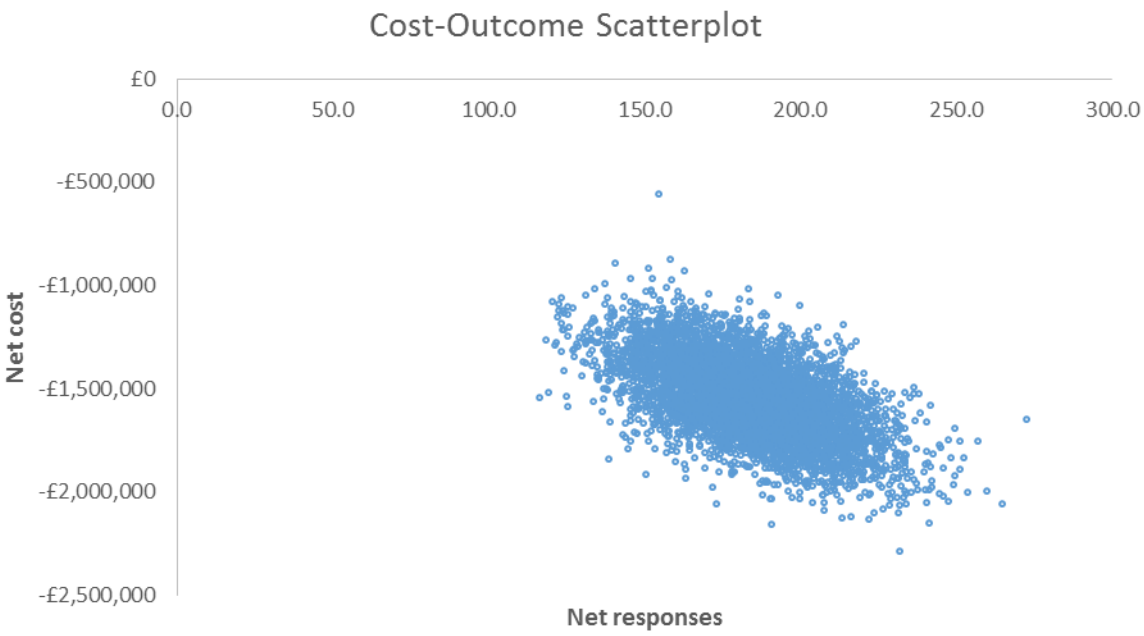

Figure 2. Costs, responses and cost outcome scatterplot of Alpha-Stim CES in relation to "Clark and Wells" model of iCBT (n=1,000 patients).

a) Costs and responses

	Expected Cost	Lower 95% CI	Upper 95% CI	Expected Responses	Lower 95% CI	Upper 95% CI
iCBT only	£4,065,532	£3,864,927	£4,276,994	701.68	649.80	750.47
AlphaStim	£2,216,601	£1,910,097	£2,725,437	889.24	859.69	907.77
Net	**-£1,848,931**	**-£2,157,449**	**-£1,353,948**	**187.56**	**142.93**	**226.91**

b) Cost outcome scatterplot

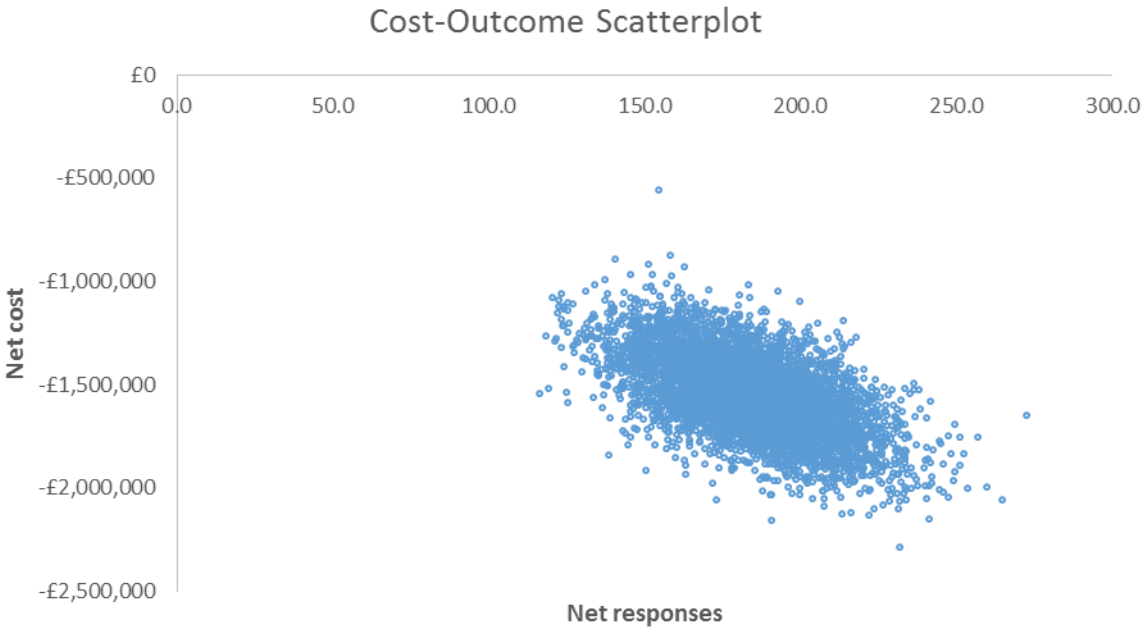

Figure 3. Costs, responses and cost outcome scatterplot of Alpha-Stim CES in relation to the "Heimberg" model of iCBT (n=1,000 patients).

a) Costs and responses.

	Expected Cost	Lower 95% CI	Upper 95% CI	Expected Responses	Lower 95% CI	Upper 95% CI
iCBT only	£2,717,082	£2,563,803	£2,875,903	701.68	649.80	750.47
AlphaStim	£1,504,619	£1,294,512	£1,876,591	889.24	859.69	907.77
Net	**-£1,212,463**	**-£1,417,929**	**-£848,589**	**187.56**	**142.93**	**226.91**

b) Cost outcome scatterplot.