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Full Study Title:

Clinical and cost effectiveness of Alpha-Stim AID Cranial Electrotherapy Stimulations (CES); a naturalistic study in patients with a primary working diagnosis of moderate-to-severe generalised anxiety disorder who did not improve with low intensity psychological therapy intervention

Short Study Title:
Clinical and cost effectiveness of Alpha-Stim AID CES

Lay Study Title:
Using a safe electronic device to help patients with anxiety disorder who did not improve with low intensity psychological therapy intervention

IRAS REFERENCE:
206555

PROTOCOL VERSION NUMBER AND DATE:
Version 2.0; 28 July 2016

SPONSOR:
Electromedical Products International, Inc.
2201 Garrett Morris Parkway
Mineral Wells
Texas
76067
United States of America

This protocol has regard for the Health Research Authority guidance and order of content.

VERSION CONTROL

Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1.0	2.0	28 July 2016	Mark Terry	Throughout: Correction of typographical mistakes. 6.1: Addition to inclusion criterion 3 of "OR deemed unsuitable for step two within an IAPT service". 7: Revised wording to clarity that 6 – 8 week waiting list is a minimum. 7.1: Revised identification process to remove follow up letter for non-responders. 7.4: Clarification of expectation of morning device use. 9.2/3: Clarification that AEs and SAEs must be recorded in the CRF. 11.2: Clarification that recruitment window if 6 months and not 12 months. 12.1: Clarification of anticipation that CRF will act as source documentation. 12.2: Clarification of email data transfer within 3 working days. Appendix B: Revised structure of CSRI but no change to content. Appendix C: Inclusion of EQ-5D-5L assessment tool.

KEY STUDY CONTACTS

Chief Investigator	**Professor Richard Morriss** University of Nottingham C20 Institute of Mental Health Jubilee Campus Wollaton Road Nottingham NG8 1BB United Kingdom Tel: 0115 823 0427 Email: Richard.Morriss@nottingham.ac.uk
Trial Co-ordinator **AND** **Sponsor Legal Representative under Research Governance Framework for Health and Social Care 2005** **AND** **Funder**	**Steve Hutchinson** The Microcurrent Site Limited 1st Floor, Unit 3 Brookside Sawtry Cambridgeshire PE28 5SB United Kingdom Tel: 01487 208041 Email: Steve@themicrocurrentsite.co.uk
Sponsor Representative	**Jeff Marksberry** Electromedical Products International, Inc

	2201 Garrett Morris Parkway Mineral Wells Texas 76967 United States of America Tel: 940 328 0788 Email: Jeff@epii.com
Key Protocol Contributors	**Dr Jennifer Martin** NIHR MindTech Healthcare Technology Co-operative The Institute of Mental Health University of Nottingham Innovation Park Triumph Road Nottingham NG7 2TU United Kingdom Tel: 0115 748 4339 Email: Jennifer.Martin@nottingham.ac.uk **Dr Peter Caunt** Nottinghamshire Healthcare NHS Foundation Trust Let's Talk Wellbeing – Leicestershire & Rutland 2 Bank Court Weldon Road Loughborough LE11 5RF United Kingdom Tel: 0115 8760174 Email: Peter.Caunt@nottshc.nhs.uk **Mark Terry** Research Applications Limited Unit 209 Pell Street Surrey Quays London SE8 5EN United Kingdom Tel: 07809 337 115 Email: Mark@researchapplications.co.uk **NIHR MindTech Healthcare Technology Co-operative** is acknowledged as having kindly facilitated the service user review.

STUDY SUMMARY

Full Study Title	Clinical and cost effectiveness of Alpha-Stim AID Cranial Electrotherapy Stimulations (CES); a naturalistic study in patients with a primary working diagnosis of moderate-to-severe generalised anxiety disorder (GAD) who did not improve with low intensity psychological therapy intervention.
Short Study Title	Clinical and cost effectiveness of Alpha-Stim AID CES.
Lay Study Title	Using a safe electronic device to help patients with anxiety disorder who did not improve with low intensity psychological therapy intervention.
Study Design	Single-centre, naturalistic post-market clinical study of one CE marked device within intended purpose over 24 week follow up period.
Study Participants	Patients seen within the three teams comprising Leicestershire and Rutland Improving Access to Psychological Therapies (IAPT) service (part of Nottinghamshire Healthcare NHS Foundation Trust) with a primary working diagnosis of moderate-to-severe generalised anxiety disorder (GAD) who did not improve (continued to have a primary working diagnosis of moderate-to-severe GAD) with previous low intensity psychological therapy intervention.
Planned Sample Size	120

Study Duration Per Participant	24 weeks	
Planned Enrolment Period	6 months from 01 September 2016 to 01 March 2017	
Planned Study End Date	01 September 2017	
Study End Definition	Last Participant Last Visit	
	Objectives	**Outcome Measures**
Primary	The primary objective of this study is to evaluate the clinical effectiveness of treatment with Alpha-Stim AID Cranial Electrotherapy Stimulations (CES) for participants with a primary working diagnosis of generalised anxiety disorder (GAD), as defined by the NHS IAPT service in terms of reliable improvement, clinically significant improvement, and recovery, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.	<u>GAD-7</u> *See Appendix A* The GAD-7 is a participant-reported screening tool and severity measure for generalised anxiety disorder (GAD). Reliable improvement is defined as participants who reach a score reduction of 5 or more from baseline to week 24. Such a reduction amounts to a clinically important change. Some reliable improvement is defined as participants who reach a score reduction of 1 – 4 from baseline to week 24. No reliable improvement is defined as participants who reach no score reduction from baseline to week 24. Clinically significant improvement is defined as participants with a score of 10 or more at baseline, who reach 9 or fewer by week 24. Recovery is defined as participants with a score of 10 or more at baseline, who reach 7 or fewer by week 24.
Secondary	The secondary objective of this study is to evaluate the cost effectiveness of treatment with	<u>Client Service Receipt Inventory (CSRI)</u>

	Alpha-Stim AID Cranial Electrotherapy Stimulations (CES) for participants with a primary working diagnosis of generalised anxiety disorder (GAD), in terms of health and social care service cost, and patient cost, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.	*See Appendix B* The CSRI, adapted for use for anxiety disorders in primary care and community settings, is a measure of the full health and social care cost and patient cost of treatment. The endpoint will be the cost impact from baseline to week 24. <u>EQ-5D-5L</u> *See Appendix C* The EQ-5D-5L is a participant-reported measure of health utility and quality of life used by NICE to generate QALYs for cost effectiveness assessments. The EQ-5D-5L uses 6 items. The endpoint will be the change in EQ-5D-5L for participants from baseline to week 24. <u>Work and Social Adjustment Scale (WASA)</u> *See Appendix D* The WASA scale is a participant-reported measure of work and social function. The WASA scale uses 5 items. The endpoint will be the change in WASA scale score for participants from baseline to week 24.
Tertiary	The tertiary objective of this study is to evaluate the clinical effectiveness of treatment with Alpha-Stim AID Cranial Electrotherapy Stimulations (CES) for depression and insomnia in participants with a	<u>PHQ-9</u> *See Appendix E* The PHQ-9 is a participant-reported measure of depressive symptomatology.

	primary working diagnosis of generalised anxiety disorder (GAD), in terms of reliable improvement, clinically significant improvement, and recovery, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.	Reliable improvement is defined as participants who reach a score reduction of 6 or more from baseline to week 24. Clinically significant improvement is defined as participants with a score of 10 or more at baseline, who reach 9 or fewer by week 24. Recovery is defined as participants with a score of 11 or more at baseline, who reach 8 or fewer by week 24. <u>Athens Insomnia Scale</u> *See Appendix F* The Athens Insomnia Scale is a participant-reported measure of sleep difficulty. Reliable improvement has no current, standardised definition, and so in this study, will be defined as participants who reach a score reduction of 50% or more from baseline to week 24. Clinically significant improvement is defined as participants with a score of 6 or more at baseline, who reach 5 or fewer by week 24. Recovery is defined as participants with a score of 6 or more at baseline, who reach 4 or fewer by week 24.
Medical Device	Alpha-Stim AID Cranial Electrotherapy Stimulations (CES) medical device, used within intended purpose (for the treatment of anxiety, depression and insomnia), under CE marking valid 12 April 2016 – 12 September 2020.	

	See Appendix H
Treatment Procedure	60-minute self-directed Alpha-Stim AID CES treatment sessions undertaken at participant's home, on a daily basis for 6 weeks for all participants. During this 6-week period, participants will be on the waiting list for high intensity psychological therapy intervention. Following 6 weeks of Alpha-Stim AID CES treatment, participants have the option to receive a further 6 weeks of treatment, which is likely to coincide with start of high intensity psychological therapy intervention as clinically indicated. Following a maximum of 12 weeks' treatment with Alpha-Stim AID CES, all participants will cease to receive treatment on study. Participants will have 1x additional visit in clinic at baseline, followed by 5 additional visits via telephone at week 4, 6, 8, 12 and 24. All participants will continue to receive standard care assessment, as undertaken by the NHS IAPT service, standard care high intensity psychological therapy intervention as clinically indicated and provided by the NHS IAPT service, and standard care pharmacological treatment as prescribed by the participant's GP. Participation in this study will not influence nor compromise standard care treatment – all study procedures are additional to standard care. Participation in the study will have no impact upon the duration of the waiting time for high intensity psychological therapy intervention.

FUNDING AND SUPPORT IN KIND

FUNDER	FINANCIAL AND NON FINANCIAL SUPPORT GIVEN
The Microcurrent Site Limited	60 Alpha-Stim AID CES devices loaned to Nottinghamshire Healthcare NHS Foundation Trust for duration of study. Should all 60 devices be in use by participants concurrently, additional devices may be loaned to the Trust. Consumables will be provided to the Trust, including AAA batteries, pregnancy testing kits, cleaning materials, conduction fluid and electrode pads. Total funding of approximately £38,000.00 to Nottinghamshire Healthcare NHS Foundation Trust for study delivery costs.

ROLE DELEGATION

SPONSOR: Electromedical Products International, Inc
Under the Research Governance Framework for Health and Social Care 2005, Electromedical Products International Inc is the legal sponsor of this research study. Electromedical Products International Inc retains responsibility for all legally mandated roles of a sponsor of clinical research, but has delegated a number of roles to the organisations listed below.

LEGAL REPRESENTATIVE AND CONTRACT RESEARCH ORGANISATION: The Microcurrent Site Limited
Under the Research Governance Framework for Health and Social Care 2005, a sponsor incorporated outside of the United Kingdom must appoint a legal representative incorporated in the United Kingdom for service of documents. Given that Electromedical Products International Inc is incorporated in the United States of America, The Microcurrent Site Limited will fulfil the role of legal representative.

In this role as legal representative, The Microcurrent Site Limited is also undertaking the following roles on behalf of the sponsor:

- Point of conduct for study conduct queries
- Upload of accrual data to the NIHR CRN Portfolio database (CPMS)
- Oversight of conduct and delivery
- Archiving
- Manuscript writing
- Dissemination of results

FUNDER: The Microcurrent Site Limited
The Microcurrent Site Limited is responsible for the provision of funding and will process and pay invoices from the NHS research site, and is also responsible for the provision of loaned medical devices and consumables.

CONTRACTED ORGANISATION: Research Applications Limited
Research Applications Limited is responsible for creation and submission of study documents to the Health Research Authority (HRA) for Research Ethics Committee (REC) favourable opinion, HRA Approval; submission to the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio; and submission to the NHS R&D department of Nottinghamshire Healthcare NHS Foundation Trust for confirmation of capacity and capability. No application to the Competent Authority is required.

LIST OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (MHRA)
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CE	Conformitee Europeenee
CES	Cranial Electrotherapy Stimulations
CPMS	Central Portfolio Management System
CRF	Case Report Form
CRN	Clinical Research Network
CRO	Contract Research Organisation
CSRI	Client Services Receipt Inventory
EU	European Union
FDA	Food and Drug Administration
GAD	Generalised Anxiety Disorder
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
IAPT	Improving Access to Psychological Therapies
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NIHR	National Institute for Health Research
PCMIS	Trust electronic patient record
PI	Principal Investigator
PIS	Participant Information Sheet
PWP	Psychological Wellbeing Practitioner
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
TMF	Trial Master File
WASA	Work and Social Adjustment Scale
WHO	World Health Organisation

STUDY FLOW CHART

Day 1 – Week 6
Initial Alpha-Stim AID CES treatment period with daily 60 minute sessions and pre and post anxiety scale completion.

Week 6 – Week 12
Optional additional Alpha-Stim AID CES treatment period with daily 60 minute sessions and pre and post anxiety scale completion.

Visit 1: Day 1
Baseline in clinic visit comprising informed consent, training in use of Alpha-Stim AID CES device, GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens and CSRI.

Visit 2: Week 4
Telephone visit comprising GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens and treatment compliance and adverse events.

Visit 3: Week 6
Telephone visit comprising GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens, CSRI and treatment compliance and adverse events.
End of treatment for participants as requested.

Visit 4: Week 8
Telephone visit comprising GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens and treatment compliance and adverse events.

Visit 5: Week 12
Telephone visit comprising GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens and treatment compliance and adverse events.
End of treatment for all participants.

Visit 6: Week 24
Telephone visit comprising GAD-7, WASA, PHQ-9, EQ-5D-5L, Athens and CSRI.
End of study for all participants.

Standard care
Participant on waiting list (at least 6 - 8 weeks) for step three high intensity psychological therapy intervention, followed by assessment and at least two individual CBT sessions as required.

1 BACKGROUND

Generalised anxiety disorder (GAD) is a common mental disorder with an annual prevalence of 2.1% to 4.4% in English speaking countries (Grant et al, 2005; Hunt et al, 2002; Kessler and Wang, 2008). Patients with a primary working diagnosis of GAD incur a significant clinical burden, and a significant cost burden upon the health and social care system. According to the World Health Organisation (WHO), anxiety disorders in general are the seventh leading cause of disability lost years in the world (Vos et al, 2012), and an economic case for the management of GAD, and other anxiety and depression disorders in working-age adults, was made by Lord Layard (Layard, 2006).

Patients with a primary working diagnosis of GAD often present with other mental disorder such as depression and insomnia, and there is strong evidence that comorbidity among anxiety, insomnia and depression is the rule, rather than the exception (Alvaro et al., 2013; Chapman et al., 2010; Soehner & Harvey, 2012; LeBlanc et al., 2009; Jansson-Frojmark & Lindblom, 2008; Buysse et al., 2008; Franzen & Buysse, 2008; Riemann, 2007; Johnson et al., 2006; Taylor et al., 2005). Comorbid anxiety and depression or insomnia can start a negative spiral in which one enhances the other (Jansson-Frojmark & Lindblom, 2008). Given that these disorders may also have a physical cause, or the symptoms of these disorders may initially be perceived as having a physical cause, the treatment of GAD and associated comorbidities can lead to considerable expenditure within a health and social care system.

NICE guidelines for the treatment of patients with a primary working diagnosis of GAD, published in England in 2011 (Nice; 2011), recommend a three step approach in the care pathway:

- Step one: Upon patient recognition of a psychological problem, and discussion with a General Practitioner (GP), the patient will receive, within primary care, an assessment/referral/active monitoring, which includes careful monitoring of symptoms, psychoeducation about the disorder, and sleep hygiene advice.

- Step two: Upon failure to improve as a result of step one treatment, the patient will be referred by a GP to an Improving Access to Psychological Therapies (IAPT) service. Alternatively, a patient may self-refer directly to an IAPT service without having undertaken step one treatment in primary care. Upon referral or self-referral, all patients will receive an assessment to diagnose their problem. If indicated, patients will receive step two treatment - the basis of step two is low intensity psychological therapy intervention, which includes individual non-facilitated self-help, individual guided self-help and psychoeducation groups. Patients are assessed throughout step two.

- Step three: Upon failure to improve as a result of step two treatments, patients will be indicated to receive from the IAPT service, as a minimum, an assessment and two individual Cognitive Behavioural Therapy (CBT) treatment sessions focussed on long-term coping strategies. Dependent upon improvement, patients will receive further CBT sessions and support as required. Pharmacological treatment, initially with selective serotonin re-uptake inhibitor anti-depressants, and subsequently drugs such as pregabalin, may be prescribed by the GP independently of the IAPT service, for which pharmacological treatment are not part of the care pathway.

Step one and two treatment are relatively inexpensive, but are often ineffective. Step three treatment, both psychological and pharmacological, are relatively expensive, requiring frequent contacts with highly qualified health professionals within the IAPT service, and prescription of expensive drugs in primary care (for example, a 28-day treatment course of pregabalin is approximately £80.00). GAD is a relatively persistent clinical problem and therefore pharmacological treatment can extend for many months and years, whilst there are frequently substantial delays in offering access to high intensity psychological treatment intervention.

Alpha-Stim AID is a CE marked medical device which has been registered as an approved product since 11 May 1998. Alpha-Stim AID 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. The treatment provided by the device is non-invasive, non-pharmacological, and can be used as adjunctive treatment to step one, two and three treatment intervention. Pregnancy, implantation with a pace maker and implantation with an implantable cardioverter device (ICD) are contraindications.

Alpha-Stim AID CES could therefore compliment psychological treatment in the IAPT care pathway, through acting as an effective maintenance treatment, and to act as adjunctive treatment to improve the clinical effectiveness of step three high intensity psychological therapy intervention. Improved effectiveness could reduce the requirement for additional psychological and pharmacological treatment, thus reducing cost within the health and social care system (primarily within the IAPT services but also within primary care), thus enabling the IAPT service to maintain capacity to deliver high intensity psychological therapy intervention.

This study will recruit 120 participants from Leicestershire and Rutland IAPT service (under the organisation of Nottinghamshire Healthcare NHS Foundation Trust). These participants will have a primary working diagnosis of moderate-to-severe GAD, and will have received step two low intensity psychological therapy intervention within an IAPT service but received no improvement (continued to be classified as moderate-to-severe GAD) from these interventions.

So as to place the study in the context of a systematic review of relevant studies, the following information provides background to the clinical effectiveness of CES treatment generally, and then specifically for anxiety, depression and insomnia.

Clinical effectiveness in general

Most early CES studies between the 1970s to early 1990s were small, had limitations and used research designs that do not meet current research standards. However, the findings from these studies were consistently positive showing that CES effectively decreased anxiety, depression and insomnia. Anxiety was the most common condition studied. A dramatic increase in the quality of CES research occurred during 1995 to 2008. The first study to use a double-blind, randomised, sham-controlled Alpha-Stim CES device protocol research design was conducted by Voris in 1995 that investigated the effectiveness of CES on anxiety in outpatient psychiatric patients. This study included 105 participants who were randomised to an active CES group (n=40) or sham CES group (n=35) 20-minute treatment, or to a control group (n=30). There was no difference among groups on the measure of anxiety at baseline, using the State Anxiety Inventory (SAI). The active CES group had significantly lower scores (indicating less state anxiety) on SAI than the sham and control groups at end point of study ($p = 0.0001$, $d = -1.60$). The active CES group had significantly higher finger temperature scores ($p = 0001$, $d = 0.50$) and significantly lower EMG scores ($p = 0.0001$, $d = -1.08$), indicating less anxiety than sham group as measured by objective physiological tests. Bystritsky et al (2008), in an open-label study was the only study in the group of CES anxiety studies that specifically looked at the efficacy of CES in participants with GAD. Anxiety scores decreased significantly from baseline to the endpoint of the study as measured by the HAMA-A ($p = 0.01$, $d = 1.52$). and the FDADS ($p = 0.01$, $d = -0.75$). A score on the CGI-I at the endpoint of the study (6 weeks), was used to determine if a participant was a responder or non-responder to treatment. At the end of the study, 6 patients (50% of the intent to treat sample and 67% of the completers) had a 50% decrease on HAMA-A and a score of 1 or 2 on the CGI-I and were therefore considered responders to treatment.

Clinical effectiveness for anxiety

There are human studies using Alpha-Stim CES technology that support the efficacy of CES for treatment of anxiety:

- 7 double-blind, sham-controlled, randomised controlled trials on anxiety using the Alpha-Stim CES technology had significant findings in favour of the treatment group (Barclay & Barclay, 2014; Kolesos, 2013; Strentzsch, 2008; Cork, 2004; Lichtbroun, 2001; Winick, 1999; and Voris 1995).
- 5 of the double-blind, sham controlled, randomised controlled trials (Barclay, 2004; Strentzsch, 2008; Cork, 2004; Lichtbroun, 2001; Winick, 1999) were replications of the Voris (1995) study using different patient populations. All of these studies found significant differences in favour of the active CES group; CES significantly decreased anxiety.
- 3 additional randomised controlled trials on anxiety found significant findings in favour of the treatment group (Lee, 2013; Kim, 2008; and Chen, 2007).
- 3 open label studies also reported that CES significantly decreased anxiety (Bystritsky, 2008; Lu, 2005 and Overcash, 1999).

Clinical effectiveness for depression

- Barclay and Barclay (2014) in a double-blind, sham-controlled, randomised controlled trial (n=115) using Alpha-Stim CES technology found that depression was significantly decreased in favour of the treatment group.
- Bystritsky et al. (2008) also reported that CES significantly decreased depression from baseline to the endpoint of the study.

Clinical effectiveness for insomnia

- 2 double-blind, sham-controlled, randomised controlled trials using Alpha-Stim CES technology found that CES significantly decreased insomnia in favour of the treatment (Taylor et al., 2013; Lichtbroun et al., 2001).
- 1 United States of America army study by Lande (2013) found Alpha-Stim CES treatment to increase sleep by 43 minutes in patients in a partial hospitalisation program after 5 days of treatment, while the sham treated group in this double-blind study reported 19 minutes less sleep.

2 RATIONALE

The purpose of this study is not demonstrate clinical effectiveness of Alpha-Stim AID CES – the device has a CE marking and there are sufficient clinical trials to demonstrate effectiveness. The purpose of this study is to address the paucity of data on the clinical effectiveness and cost effectiveness in an NHS setting. For Alpha-Stim AID CES treatment to be available as standard care within the IAPT service, the treatment must be appraised by NICE, which will require evidence of clinical effectiveness in the NHS, and an assessment of the economic impact.

The study will also be published to demonstrate to an international audience of how Alpha-Stim AID CES can complement psychological therapy intervention within a care pathway, which may then be commissioned in other health and social care systems. However, the study is primarily designed to obtain sufficient evidence for NICE and NHS England.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary objective

The primary objective of this study is to evaluate the clinical effectiveness of treatment with Alpha-Stim AID cranial electrotherapy stimulations (CES) for participants with a primary working diagnosis of generalised anxiety disorder (GAD), as defined by the NHS IAPT service in terms of reliable improvement, clinically significant improvement, and recovery, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.

3.2 Secondary objectives

The secondary objective of this study is to evaluate the cost effectiveness of treatment with Alpha-Stim AID cranial electrotherapy stimulations (CES) for participants with a primary working diagnosis of generalised anxiety disorder (GAD), in terms of health and social care service cost, and patient cost, over the previous 12 weeks, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.

3.3 Tertiary objective

The tertiary objective of this study is to evaluate the clinical effectiveness of treatment with Alpha-Stim AID cranial electrotherapy stimulations (CES) for depression and insomnia in participants with a primary working diagnosis of Generalised Anxiety Disorder (GAD), in terms of reliable improvement, clinically significant improvement, and recovery, from baseline to week 24, following previous treatment with low intensity psychological therapy intervention.

3.4 Primary outcome measures

The primary objective will be measured using GAD-7 scores, which is a participant-reported screening tool and severity measure for generalised anxiety disorder (GAD).

- The outcome measure for **reliable improvement of GAD** is defined as participants who reach a score reduction of 5 or more from baseline to week 24. Such a reduction amounts to a clinically important change. Some reliable improvement is defined as participants who reach a score reduction of 1 – 4 from baseline to week 24. No reliable improvement is defined as participants who reach no score reduction from baseline to week 24.
- The outcome measure for **clinically significant improvement of GAD** is defined as participants with a score of 10 or more at baseline, who reach 9 or fewer by week 24.
- The outcome measure for **recovery of GAD** is defined as participants with a score of 10 or more at baseline, who reach 7 or fewer by week 24.

3.5 Secondary outcome measures

The secondary objective will be measured using the Client Service Receipt Inventory (CSRI), adapted for use for anxiety disorders in primary care and community settings, which is a measure of the full health and social care cost and patient cost of treatment. Additionally, the objective will be measured using the EQ-5D-5L, which is a participant-reported measure of health utility and quality of life used by NICE to generate QALYs for cost effectiveness assessments, and uses 6 items. Finally, the objective will be measured using the Work and Social Adjustment Scale (WASA) which is a participant-reported measure of work and social function, and uses 8 items.

- The outcome measure for **CSRQ** is the change in cost impact for previous 12 weeks from baseline to week 24.
- The outcome measure for **EQ-5D-5L** is the change for participants from baseline to week 24.
- The outcome measure for **WASA** is the change for participants from baseline to week 24.

3.6 Tertiary outcome measures

The tertiary objectives will be measured using the PHQ-9, which is a participant-reported measure of depressive symptomatology. Additionally, the objective will be measured using the Athens Insomnia Scale, which is participant-reported measure of sleep difficulty.

- The outcome measure for **reliable improvement of depressive symptomology** is defined as participants who reach a score reduction of 6 or more from baseline to week 24.
- The outcome measure for **clinically significant improvement of depressive symptomology** is defined as participants with a score of 10 or more at baseline, who reach 9 or fewer by week 24.
- The outcome measure for **recovery of depressive symptomology** is defined as participants with a score of 11 or more at baseline, who reach 8 or fewer by week 24.

- The outcome measure for **reliable improvement of insomnia** has no current, standardised definition, and so in this study, will be defined as participants who reach a score reduction of 50% or more from baseline to week 24.
- The outcome measure for **clinically significant improvement of insomnia** is defined as participants with a score of 6 or more at baseline, who reach 5 or fewer by week 24
- The outcome measure for **recovery of insomnia** is defined as participants with a score of 6 or more at baseline, who reach 4 or fewer by week 24.

4 STUDY DESIGN

This is a single-centre, naturalistic post-market clinical study of one CE marked device within intended purpose over 24-week follow-up period. The study will enrol patients with a primary working diagnosis of moderate-to-severe GAD who did not improve (continued to have a primary working diagnosis of moderate-to-severe GAD) with previous low intensity psychological therapy intervention.

Participants indicated for high intensity psychological therapy intervention will be approached by their routine care provider (either a Psychological Wellbeing Practitioner (PWP) or Cognitive Behavioural Therapist) with information about this study when they are contacted to discuss a step-up to step 3 high intensity therapy. From this initial approach, the current minimum waiting time for access to such therapy interventions is at least 6 - 8 weeks.

Participants who consent to enrolment will undertake 60 minute self-directed Alpha-Stim AID CES treatment sessions in their own homes on a daily basis for 6 weeks. During this 6-week period, participants will be on the waiting list for high intensity psychological therapy intervention.

Following 6 weeks of Alpha-Stim AID device treatment, participants have the option to receive a further 6 weeks of treatment, which may coincide with start of high intensity psychological therapy interventions as clinically indicated. This option is available to make the study design more comparable to real-world scenarios.

Participants wishing to discontinue use of the Alpha-Stim AID device will return the device and any unused electrode pads to the research nurse via pre postage paid envelope.

Following a maximum of 12 weeks' treatment with Alpha-Stim AID device, all participants will cease to receive treatment on study. At this time-point, all participants will return the device and any unused electrode pads to the research nurse via pre postage paid envelope.

Participants will have 1x additional visit in clinic at baseline, followed by 5 additional visits via telephone at week 4, 6, 8, 12 and 24.

All participants will continue to receive standard care assessment, as undertaken by the NHS IAPT service, standard care high intensity psychological therapy intervention as clinically indicated and provided by the NHS IAPT service, and standard care pharmacological treatment as prescribed by the participant's GP. Participation in this study will not influence nor compromise standard care treatment – all study procedures are additional to standard care. Participation in the study will have no impact upon the duration of the waiting time for high intensity psychological therapy intervention.

5 STUDY SETTING

Participants will be enrolled from the clinical caseload of the three teams comprising Leicestershire and Rutland Improving Access to Psychological Therapies (IAPT) service (part of Nottinghamshire Healthcare NHS Foundation Trust). These participants will have 1x additional baseline visit in clinic (which will be the routine facilities of the IAPT service, comprising a GP clinic room or community venue) in addition to 5x additional visits via telephone at week 4, 6, 8, 12 and 24.

Participants will continue to receive standard of care assessments and interventions as routine, which will take place in routine facilities.

Study delivery will be undertaken by staff within the IAPT service, in addition to staff from NIHR CRN East Midlands.

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Primary working diagnosis of moderate-to-severe GAD indicated via a GAD-7 score of 10 or more at baseline visit
- Previous treatment within an IAPT service with step two low intensity psychological therapy intervention
- Indicated for step three high intensity psychological therapy intervention and on the waiting list OR deemed unsuitable for step two within an IAPT service
- Capable of giving informed consent
- Female participants of child-bearing potential must have a negative urine human chorionic gonadotropin dipstick pregnancy test
- Female participants of child-bearing potential must be practising a highly effective method of contraception (failure rate of less than 1% per year when used consistently and correctly and agree to remain on a highly effective method throughout the 6 or 12 week treatment period. Examples of highly effective contraceptives include: barrier condoms, intrauterine device (IUD), intrauterine hormone-

releasing system (IUS), vasectomised partner, sexual abstinence (refraining from heterosexual intercourse), and oestrogen and progestogen containing hormonal contraception associated with ovulation.

- 18 years of age or above at baseline visit
- Able to understand written and verbal English

6.2 Exclusion criteria

- Primary working diagnosis of a mental disorder other than moderate-to-severe GAD (but other mental and anxiety disorders as secondary comorbidities is not an exclusion criteria)
- No previous treatment within an IAPT service with step two low intensity psychological therapy intervention
- Not indicated for step three high intensity psychological therapy intervention and not on the waiting list
- Requiring urgent clinical care
- Female participants of child-bearing potential with a positive urine human chorionic gonadotropin dipstick pregnancy test
- Female participants of child-bearing potential not willing to practice a highly effective method of contraception during the treatment period
- Implantation with a pace maker
- Implantation with an implantable cardioverter defibrillator (ICD)
- Incapable of giving informed consent
- 17 years of age or less at baseline visit
- Unable to understand written and verbal English

7 STUDY PROCEDURES

Participants will have study specific assessments, undertaken at additional visits at day 1, week 4, week 6, week 8, week 12 and week 24, in addition to self-directed treatment with Alpha-Stim AID CES for a minimum of 6 weeks and a maximum of 12 weeks.

Whilst enrolled in the study, participants will be on the waiting list for high intensity psychological therapy intervention, and may begin to receive such interventions if clinically indicated following the minimum 6 - 8 week waiting period. Scores from assessments undertaken for the purposes of this study will be available to the IAPT service and may be used to inform treatment plans.

7.1 Participant Identification

Eligible participants will be known to the IAPT service, as these patients will have been indicated for step three high intensity psychological therapy intervention, and will be on the waiting list. As per standard care, during step two low intensity psychological therapy intervention, as provided by the PWP or Cognitive Behavioural Therapist within the IAPT service, patients will be assessed. Those who have not improved as a result of treatment (due to a GAD-7 score remaining at 10 or above and therefore remaining to be moderate-to-severe) will be contacted by the routine PWP or Cognitive Behavioural Therapist at a face-to-face visit, via telephone, via email and/or via letter to discuss a step-up to step three therapy intervention.

As such, all PWPs and Cognitive Behavioural Therapists in the IAPT service will screen their patient lists pro-actively to maintain an awareness of those patients who are eligible. Concurrently to receiving information about a step-up to step three therapy intervention, patients will receive a Participant Information Sheet (PIS) to introduce and explain the study. As such, the initial approach will be from a member of the patient's routine healthcare team. Patients must respond to the PWP or Cognitive Behavioural Therapist to advise that they do

not wish to be placed on to the waiting list for step three. For any patients that are currently on the waiting list, the PWP or Cognitive Behavioural Therapist will contact the patient with a Participant Information Sheet (PIS) to introduce and explain the study.

The PIS will encourage patients that are interested in learning more about this study to contact the research nurse assigned to study delivery, by telephone, email or post. The research nurse will be employed by NIHR CRN East Midlands to assist with study delivery. Patients that do not respond will be deemed uninterested in study participation. The PWP or Cognitive Behavioural Therapist will maintain a screening log to record those patients who have been approached about study participation. The research nurse will therefore have no contact with any patient who has not indicated consent to discuss the study, and as such, no access to personal identifiable information prior to the patient themselves making contact.

No participants will be identified at any other services other than via the three teams comprising Leicestershire and Rutland IAPT service. No participants will be identifiers via Participant Identification Centres (PICs) and no participants will have the opportunity to self-refer as none will be recruited by publicity.

7.2 Consent

Following the initial approach, and once a patient has contacted the research nurse to learn more about the study, a baseline visit will be arranged for the patient to further discuss the study and consent. The baseline visit will be an additional visit, and will take place at routine facilities used by the IAPT service (either a GP clinic room or community venue).

Patients will have the opportunity to discuss the details of the study with the research nurse, and if happy to proceed, will sign the Informed Consent Form (ICF). If a patient would not like to participate following a discussion of the study with the research nurse, their involvement will terminate at this time point and they will continue to receive routine care. The research nurse will evaluate the capacity of the patient to consent at this time point. Should the research nurse not be content that the patient fully understands the study, and is therefore able to make an informed decision regarding participation, then the patient will not be enrolled.

One copy of the ICF will be received by the participant, one copy will be stored in the Investigator Site File (ISF) and one copy will be scanned into PCMIS - the electronic patient record system used locally.

It will be made clear that all participants will continue to receive standard care assessment, as undertaken by the NHS IAPT service, standard care high intensity psychological therapy intervention as clinically indicated and provided by the NHS IAPT service, and standard care pharmacological treatment as prescribed by the participant's GP. Participation in this study will not influence nor compromise standard care treatment – all study procedures are additional to standard care. Participation in the study will have no impact upon the duration of the waiting time for high intensity psychological therapy intervention.

7.3 Screening

Participants will have a confirmed working diagnosis of moderate-to-severe GAD via a GAD-7 score of 10 or more upon identification by the PWP or Cognitive Behavioural Therapist as potentially eligible for the study.

Once the ICF has been signed, the research nurse will take a urine pregnancy dipstick test for any female participant of child-bearing potential. Should the result be positive, their involvement will terminate at this time-point and they will continue to receive routine care.

It is possible that, over the timeframe of having been identified and provided consent to participate, the GAD-7 score of the participant may have changed. As such, once the ICF has been signed, the research nurse, trained in the administration of the GAD-7, will undertake a GAD-7 assessment with the participant. Should the participant, at this baseline visit, have a score of 9 or less, their involvement will terminate at this time point and they will

continue to receive routine care. The research nurse will also re-confirm full eligibility in accordance with the inclusion/exclusion criteria.

This baseline visit will be the sole additional in-clinic visit, with all other study visits undertaken via telephone. Patients that attend this baseline visit will have their travel expenses reimbursed up to a maximum of £10.00 and must submit their receipt(s) or indication of miles driven (reimbursement up to £0.45 per mile in accordance with HMRC guidance). Patients will receive this reimbursement in cash at the baseline visit.

7.4 Baseline assessments

Baseline visit 1: Day 1

Having provided consent for participation, the research nurse will notify the participant's GP via a notification letter unless the participant expressly requests that the GP is not notified, and the research nurse will undertake the following assessments:

Urine pregnancy test

The first assessment will be a urine pregnancy dipstick human chorionic gonadotropin test will be used to assess pregnancy in all females of child-bearing potential. The urine and dipstick will be disposed of in accordance with the Human Tissue Authority code of conduct.

GAD-7

See Appendix A

The second assessment will be the GAD-7, which is a participant-reported screening tool and severity measure for generalised anxiety disorder (GAD). The GAD-7 score is calculated by assigning scores of 0, 1, 2 and 3, to the responses categories of "not at all", "several days", "more than half the days" and "nearly every day", respectively to 7 problems over the last 2 weeks, and adding together the scores for the 7 problems. The maximum score is 21. Scores of 5, 10 and 15 are taken as the cut-off points for mild, moderate and severe anxiety.

The research nurse will administer the GAD-7 and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 5 minutes.

Client Service Receipt Inventory (CSRI)

See Appendix B

The CSRI, for use for anxiety disorders in primary care and community settings, is a measure of the full health and social care cost and patient cost of treatment.

The research nurse will administer the CSRI and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 15 minutes.

EQ-5D-5L

See Appendix C

The EQ-5D-5L is a participant-reported measure of health utility and quality of life used by NICE to generate QALYs for cost effectiveness assessments. The EQ-5D-5L uses 6 items, covering the categories of mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a visual analogue score of health state.

The research nurse will administer the EQ-5D-5L and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 5 minutes.

Work and Social Adjustment Scale (WASA)

See Appendix D

WASA scale is a participant-reported measure of work and social function. The WASA scale uses 5 items, covering the categories of work, home management, social leisure activities, private leisure activities, and family and relationships, to the response categories of “not at all”, “slightly”, “definitely”, “markedly”, “very severely”. The maximum score is 40.

The research nurse will administer the WASA and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 5 minutes.

PHQ-9

See Appendix E

The PHQ-9 is a participant-reported measure of depressive symptomatology. The PHQ-9 uses 9 items, to the response categories of “not at all”, “several days”, “more than half the days”, and “nearly every day”. The maximum score is 27.

The research nurse will administer the PHQ-9 and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 5 minutes.

Athens Insomnia Scale

See Appendix F

The Athens Insomnia Scale is a participant-reported measure of sleep difficulty. Athens scale used 8 items, covering the categories of sleep induction, awakening during the night, final awakening earlier than desired, total sleep duration, overall quality of sleep, sense of well-being during the day, functioning (physical and mental) during the day, and sleepiness during the day, to 5 response categories. The maximum score is 24.

The research nurse will administer the Athens scale and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that this assessment will take approximately 5 minutes.

Alpha-Stim AID CES treatment

Participants will be trained in the use of the Alpha-STIM AID medical device by the research nurse, and will be informed that they are expected to undertake 60-minute self-directed Alpha-Stim AID CES treatment sessions undertaken at their home, on a daily basis for 6 weeks. It is expected that participants will use the device in the morning if possible. Participants will receive a written instruction sheet and will be advised to contact the research nurse if they have any queries. Participants will use ear clip electrodes with the current set at their level of comfort.

Participants will undertake all sessions at home, and none in-clinic. Immediately prior to treatment, and post treatment, participants will record their level of anxiety of a scale of 0 – 10 (with 0 indicating no anxiety and 10 maximum anxiety). Participants will record these measurements in a log, which will act as source data.

See Appendix G.

The first treatment session should be completed after the baseline assessments undertaken by the research nurse.

During this 6-week period, participants will be on the waiting list for high intensity psychological therapy intervention.

Following 6 weeks of Alpha-Stim AID CES treatment, participants have the option to receive a further 6 weeks of treatment, which is likely to coincide with start of high intensity psychological therapy intervention as clinically indicated.

Following a maximum of 12 weeks' treatment with Alpha-Stim AID CES, all participants will cease to receive treatment on study.

7.5 Study assessments

At baseline, participants will agree with the research nurse a convenient time and date for the visits undertaken via telephone. Visits should be undertaken within 5 calendar days of the exact date.

Additional visits are undertaken at 4 weeks post baseline, 6 weeks post baseline, 8 weeks post baseline, 12 weeks post baseline and 24 weeks post baseline.

Visit 2: Week 4 (plus or minus 5 calendar days)

The research nurse will telephone call the participant and undertake the following assessments:

- GAD-7
- EQ-5D-5L
- WASA
- PHQ-9
- Athens Insomnia Scale
- Check treatment compliance and anxiety log completion
- Check adverse events

The research nurse will administer these and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that these assessments will take approximately 30 minutes in total.

Visit 3: Week 6 (plus or minus 5 calendar days)

The research nurse will telephone call the participant and undertake the following assessments:

- GAD-7
- EQ-5D-5L
- WASA
- PHQ-9
- Athens Insomnia Scale
- Check treatment compliance and anxiety log completion
- Check adverse events

The research nurse will administer these and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that these assessments will take approximately 30 minutes in total.

At this visit, the research nurse will discuss whether the participant wishes to continue with Alpha-Stim AID CES treatment in the same manner for an additional 6 weeks. If the participant does wish to do so, they will be advised that they must continue to complete the anxiety log book. The decision to continue or end treatment with Alpha-Stim AID CES will not impact upon access to stand care therapy interventions, and participants will be contacted by the IAPT service regardless of their decision at this time point. If the participant does not wish to continue with Alpha-Stim AID CES treatment, the research nurse will ask that they return the medical device via post.

The final treatment session should be completed immediately prior to the visit 3 assessments undertaken by the research nurse.

Visit 4: Week 8 (plus or minus 5 calendar days)

The research nurse will telephone call the participant and undertake the following assessments:

- GAD-7

- EQ-5D-5L
- WASA
- PHQ-9
- Athens Insomnia Scale
- Check treatment compliance and anxiety log completion (if continuing with Alpha-Stim AID CES treatment)
- Check adverse events (if continuing with Alpha-Stim AID CES treatment)

The research nurse will administer these and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that these assessments will take approximately 30 minutes in total.

Visit 5: Week 12 (plus or minus 5 calendar days)

The research nurse will telephone call the participant and undertake the following assessments:

- GAD-7
- EQ-5D-5L
- WASA
- PHQ-9
- Athens Insomnia Scale
- CSRI
- Check treatment compliance and anxiety log completion (if continuing with Alpha-Stim AID CES treatment)
- Check adverse events (if continuing with Alpha-Stim AID CES treatment)

The research nurse will administer these and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that these assessments will take approximately 45 minutes in total.

At this visit, the participant will end treatment with Alpha-Stim AID CES and the research nurse will ask that they return the medical device via post.

The final treatment session should be completed immediately prior to the visit 5 assessments undertaken by the research nurse.

Visit 6: Week 24 (plus or minus 5 calendar days)

The research nurse will telephone call the participant and undertake the following assessments:

- GAD-7
- EQ-5D-5L
- CSRI

- WASA
- PHQ-9
- Athens Insomnia Scale

The research nurse will administer these and record the data either directly into the electronic patient record (PCMIS) if available (and therefore the PCMIS record will act as source data), or into a Case Report Form (CRF) if not available (and therefore the CRF will act as source data) and then transpose the data into PCMIS or scan the CRF into the electronic file.

It is anticipated that these assessments will take approximately 30 minutes in total.

This is the end of study visit, after which the participant will cease communication with the research nurse.

7.6 Assessment summary

ASSESSMENT	VISIT 1 DAY 1	VISIT 2 WEEK 4	VISIT 3 WEEK 6	VISIT 4 WEEK 8	VISIT 5 WEEK 12	VISIT 6 WEEK 24
CONSENT	X					
TRAINING IN USE OF ALPHA STIM AID	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
ATHENS	X	X	X	X	X	X
ALPHA-STIM AID CES TREATMENT	Ongoing	Ongoing	Ongoing (**)	Ongoing (**)	Ongoing (**)	
COMPLIANCE		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.

7.7 Follow up

If a participant is unavailable for the pre-arranged telephone call visit, and the visit is likely to fall outside of the 5 calendar day window, the sponsor legal representative must be informed.

If a participant is lost to follow up during the Alpha-Stim AID CES treatment period, or during the follow up period, best efforts should be made to re-establish contact by the research nurse, in conjunction with the IAPT service, to ensure return of the medical device and full data collection.

7.8 Withdrawal

Participants will be made aware that they are free to withdraw from the study at any time point, without giving reason. If participants withdraw during the Alpha-Stim AID CES treatment period, the participant should return the medical device and any unused electrodes to the research nurse. Participants will be informed that the data collected prior to their withdrawal will be retained for analysis unless a specific request is made for their data to be removed from analysis.

Participants may be withdrawn from the study, if it is in the best interests of the participant, in the view of the Principal Investigator.

7.9 End of study

Participants will be enrolled in the study for 24 weeks from baseline, with the recruitment window anticipated to open 01 September 2016 and close 01 March 2017. The end of study is defined as last participant last visit, and this is anticipated at 01 September 2017. The REC will be notified of the end of study.

8 STUDY DEVICE

8.1 Nature of device

The medical device is the Alpha-Stim AID CES device, which will be used within intended purpose (for the treatment of anxiety, depression and insomnia), under CE marking valid 12 April 2016 – 12 September 2020.

See Appendix H.

8.2 End of study provision

The device is marketed and sold in the UK by the sponsor legal representative, and are available from private purchase at a cost of £499.00. Participants will be fully informed that participation in the study will result in a maximum of 12 weeks of Alpha-Stim AID device treatment, after which time point the device must be returned to the research nurse. Participants will not be encouraged to purchase a device, but will be advised by the research nurse if an interest is expressed. Participants will not receive a discount on the purchase of a device.

8.3 Storage and handling on device

60 Alpha-Stim AID CES medical devices will be provided to site in one single bulk dispatch, and will be loaned for the period of the study. All 60 medical devices are expected to be returned to the sponsor legal representative by the end of the study. The devices should be kept in secure location until given to participants, for use in their homes, for the 6 or 12 week treatment period. Should all 60 devices be in use by participants concurrently, additional devices may be loaned.

The sponsor is not listed on the NHS Master Indemnity Agreement register, and therefore a Form of Indemnity will be signed between the sponsor as the device supplier and the site to provide confirmation that there is adequate public and product liability insurance in place for £1,000,000.00.

See Appendix I

The site will not be held liable for maintenance and cleaning costs, wear-and-tear, accidental damage and loss of these devices.

8.4 Safety profile

CES is the application of a pulsed, mild electrical current to the head using ear clip electrodes (0.5 Hz, 50% duty cycle, and 100 to 500 μA). The U.S. Food and Drug Administration (FDA) cleared CES for the treatment of anxiety, depression and insomnia in 1979. CES is non-invasive and has an excellent safety profile. A FDA commissioned review of the safety of CES by the National Research Council (1974) stated, "significant side effects or complications attributable" to the application of electric current of approximately one milliampere or less for "therapeutic effect to the head" (i.e., cranial electrotherapy stimulation) were "virtually non-existent". The Alpha-Stim AID uses 50% of this amount of current at the highest CES setting. A review of 14 Alpha-Stim CES studies using human subjects revealed that incidence of adverse events was < 1% and all were mild and self-limiting. Between 2007 and 2011, there was a total of 8,248,920 Alpha-Stim CES treatments (1,982,520 individual users treatments plus 6,266,400 in-office treatments by practitioners) based on the sales figures for 2007 - 2011 of 58,030 minus returns (there were 75 returns in 2011), an individual home Alpha-Stim post-marketing user survey (EPI, 2011a) and an Alpha-Stim practitioner survey (EPI, 2011b)**.**

14 adverse events were reported 2007 – 2011, comprising skin irritation at electrode site (11), tinnitus (2) and panic attack (1).

No serious adverse events have been reported during the 33 years that Alpha-Stim CES had been on the market.

9 SAFETY REPORTING

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant receiving treatment with Alpha-Stim AID CES, including occurrences which are not necessarily caused by or related to that product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect

9.2 AE reporting

The purpose of this study is not demonstrate clinical effectiveness of Alpha-Stim AID CES, which has been established. However, AEs should be recorded in PCMIS and reported to the CI or sponsor legal representative via completion of the CRF upon the research nurse becoming aware of these.

9.3 SAE reporting

SAEs should be recorded in PCMIS and the CRF, and reported to the CI or sponsor legal representative via telephone and email upon the research nurse becoming aware of these. The CI or sponsor legal representative will notify the REC which issued favourable opinion within 15 days of becoming aware of the event using the HRA SAE report form for non-CTIMPs.

9.4 Urgent safety measures

The CI or sponsor legal representative will notify the REC which issued favourable opinion immediately by telephone or within 3 days in writing of the implementation of an urgent safety measure and the plan for further action.

9.5 Pregnancy reporting

A urine pregnancy dipstick human chorionic gonadotropin test will be used to assess pregnancy in all females of child-bearing potential at baseline. Pregnancy should be recorded in PCMIS and reported to the CI or sponsor legal representative via email upon the research nurse becoming aware of these and a decision will be made regarding continued participation.

Pregnancy is an exclusion criterion and reportable as a precautionary measure as research has not been undertaken on the safety and efficacy of Alpha-Stim AID CES treatment in pregnant patients.

10 PROGRESS REPORTING

10.1 Progress reports

The CI or sponsor legal representative will submit, annually, starting at 12 months' post-date of favourable opinion, a progress report to the REC which issued favourable opinion, using the HRA progress report from for non-CTIMPs.

10.2 Declaration of conclusion

The CI or sponsor legal representative will submit, within 90 days of study end, a declaration of study conclusion, to the REC which issued favourable opinion, using the HRA standard form.

10.3 Summary of final report

The CI or sponsor legal representative will submit, within one year of study end, a summary of final report, to the REC which issued favourable opinion. The summary will be posted online by the HRA. It is intended that the final report will be presented at conference and published, but will primarily be used to obtain sufficient evidence for NICE and NHS England approval.

11 STATISTICS AND DATA ANALYSIS

11.1 Sample size calculation

If Alpha-Stim AID CES has a comparable effect to IAPT high intensity psychological therapy interventions in patients with a primary working diagnosis of GAD, it will achieve an effect size of 1.04 (95% CI 0.88 to 1.23) in an intention to treat sample of 4,183 participants with pre-treatment GAD-7 score of 14.06 (s.d. 5.11) and post treatment GAD-7 score of 8.10 (s.d. 6.37) (Richards and Borglin, 2011). Reliable improvement was obtained after IAPT treatment for generalised anxiety disorder in 54.7%, reliable improvement plus clinically significant change in 40.1% and recovery in 46.0%.

However, to make a meaningful economic impact on NHS care, then Alpha-Stim AID CES does not need to be as effective as IAPT high intensity psychological therapy interventions. In a previous randomised controlled trial (Barclay and Barclay 2014), Alpha Stim CES reduced the mean Hamilton Anxiety score from 29.5 to 13.4 while sham Alpha Stim CES reduced it from 27.6 to 20.0 over 5 weeks p=0.001, d=0.94, with 83% patients showing a drop of 50% in HAM-A score.

A meta-analysis of 14 Alpha Stim CES randomised controlled trials estimates an average effect size of 0.60. On this basis reliable improvement may be seen in 33%, reliable improvement plus clinically significant change in 24% and recovery in 28% cases.

The cost of IAPT high intensity psychological therapy intervention is estimated to be £2,895.00 per participant and £2,914.00 if stepped care was involved (Radhakrishnan et al, 2013). On a cost offset basis if Alpha-Stim AID CES cost £465.00, then reliable improvement plus clinically significant change (which would not necessitate high intensity treatment) in only 20% would be clinically and cost effective.

Taking all data into account, 60 patients would be required to complete Alpha Stim AID CES treatment and all assessments. However, to allow for drop-out from assessments, drop-out from Alpha-Stim AID CES, and choice in relation to IAPT high intensity psychological therapy intervention ,120 patients will be recruited.

It is anticipated from a sample size of 120, then at least 40 (33%) would show reliable improvement, 29 (24%) plus clinically significant improvement, and 34 (28%) recovery at 6 months. Since a repeat course of Alpha-Stim from 6 to 12 weeks can result in further improvement in those who have made some improvement in symptoms, we estimate that a further 20 (17%) will make a reliable improvement in their symptoms. Therefore, it is anticipated that 60 (50%) will make a reliable improvement in their GAD-7 symptoms requiring no additional psychological treatment or a minimal psychological treatment intervention (in those with other symptoms or do not make a reliable improvement plus clinically significant change).

11.2 Planned recruitment rate

According to IAPT service data, 11.7% cases referred to IAPT meet criteria to establish a primary working diagnosis GAD. Of these 39.1% make no clinical improvement and are still clinical cases with a primary working diagnosis of GAD upon completion of low intensity psychological therapy intervention (Richards and Borglin, 2011). On this basis 4.6% of all referrals to the three teams within the single IAPT service should be eligible so a conservative estimate is that 2.0% of all referrals may be recruited to this study, allowing for exclusions and 50% consent to participation. The IAPT service receives 11,000 referrals per year each leading to 440 potential participants.

It is planned that recruitment will be complete within 6 months.

11.3 Statistical analysis plan

Mean and standard deviation scores will be reported for each visit time-point. The statistician who will deliver the analysis is:

Larry R. Price, Ph.D., PStat
Professor – Psychometrics & Statistics
Accredited Professional Statistician - American Statistical Association
Director – Initiative for Interdisciplinary Research Design & Analysis (IIRDA)
Texas State University
San Marcos, Texas 78666
Email: lprice@txstate.edu

12 DATA HANDLING

12.1 Data collection tools and source document identification

The data collection tools are:

- GAD-7
- EQ-5D-5L
- CSRI
- WASA
- PHQ-9
- Athens Insomnia Scale
- Anxiety log

The research nurse will administer these and record the data as follows:

- Enter the data directly into the electronic patient record (PCMIS) – GAD-7, WASA and PHQ-9 are currently established within PCMIS. In this scenario, PCMIS record acts as the source document. A copy of the anonymised PCMIS data will then be emailed to the sponsor.
  OR
- Enter the data into a CRF – EQ-5D-5L, CSRI, and Athens are not currently established within PCMIS. In this scenario, the CRF acts as the source document. The source document will be scanned into PCMIS, and a copy will then be emailed to the sponsor. It is anticipated that the CRF will act as source documentation for all assessments, regardless of establishment within PCMIS.
  OR
- Participant will enter data into the anxiety log, and send this to the research nurse at week 6 or week 12. The anxiety log will act as the source document, and will be scanned into PCMIS, and a copy will then be emailed to the sponsor.

12.2 Data handling and record keeping

Participant in the study will be confidential. Only IAPT staff who are part of the patient's routine care team will have access to personal information prior to the patient indicating interest in the study and arranging a baseline visit with the research nurse.

When consent is received, participants will ask to agree for IAPT staff, host institution, authorised representatives of the Sponsor and regulatory authorities to have access to participant's medical records for the purpose of monitoring and audit.

Source data will be retained at site, and copies will be sent in hard copy via email to the Sponsor, whereby data will be inserted into the study database. Study database will be maintained by the Sponsor, and will be stored anonymously at all times. It will not be possible to identify participants from the information stored, and no identifiable information will be used in any publications. Data will be emailed within 3 working days of the participant visit.

12.3 Archiving

The TMF will be retained by the sponsor legal representative, and the ISF will be retained by the host site. Both the TMF and ISF must be archived for a minimum of five years post study end date. Sponsor legal representative will notify the host site when essential documents may be destroyed.

13 AUDIT

Data will be monitored for quality by the sponsor, sponsor legal representative or delegated representative throughout the study to ensure consistent data collection.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Approvals

Prior to enrolling participants, the study will be submitted to the HRA for REC and legislation compliance reviews. The study will not enrol participants until receipt of REC favourable opinion, HRA Approval, and local confirmation of capacity and capability from Nottinghamshire Healthcare NHS Foundation Trust. Competent Authority approval is not required.

The study will comply with all approval requirements, including the requirement for registration to a publically accessible database. The study will be registered to clinicaltrials.gov within 6 weeks of recruitment of the first participant.

14.2 Peer review

The study has been subject to expert peer review within the sponsor organisation. The review has been undertaken by a member of the organisation who is independent of the research team and independent of the financial team. The review indicates that the aims and objectives are achievable based upon the design and methodology.

14.3 Public and patient involvement

Sponsor recognises the value of patient and public involvement, and therefore service users have been involved in the design of the research, to review and improve the protocol design and participant information sheet design. This involvement was kindly facilitated by NIHR MindTech Healthcare Technology Co-operative.

14.4 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Accidental protocol deviations can happen, and the research nurse should adequately document these and report to the CI and sponsor legal representative immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.5 Notification of serious breaches to GCP and/or the protocol

A serious breach is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the participants
- The scientific value of the study

The CI and sponsor legal representative will be notified immediately of any case where the above definition applies during the study, and immediate action will be undertaken.

14.6 Data protection and patient confidentiality

All investigators and host site staff must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

Participants will be assigned a coded, depersonalised study ID upon consent. The study ID will be used on all documentation emailed to the sponsor. The sponsor will never receive personally identifiable data. The linking document between the code and the participant's identifying information will be retained at the host site. The custodian of the data remains the Caldicott Guardian within Nottinghamshire Healthcare NHS Foundation Trust.

14.7 Financial and other competing interests

Host site (Nottinghamshire Healthcare NHS Foundation Trust) will receive payment for enrollment of participants in the study, in accordance with the negotiated fee outlined in the NIHR CRN Industry Costing Template.

Neither the CI, PI nor host site staff have any commercial ties to the Sponsor nor Sponsor's Legal Representative.

14.8 Indemnity

Sponsor has sufficient indemnity in place for the management and design of the study, and NHS indemnity will be in place for the conduct of the study at the host site.

14.9 Amendments

Amendments will be notified to the HRA, REC and host site as per requirements under UK procedures.

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16 APPENDIX A: GAD-7

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1 Feeling nervous, anxious or on edge	0	1	2	3
2 Not being able to stop or control worrying	0	1	2	3
3 Worrying too much about different things	0	1	2	3
4 Trouble relaxing	0	1	2	3
5 Being so restless that it is hard to sit still	0	1	2	3
6 Becoming easily annoyed or irritable	0	1	2	3
7 Feeling afraid as if something awful might happen	0	1	2	3

GAD7 total score ☐

(Data item 38 in the IAPT Data Standard)

17 APPENDIX B: CSRI

Ethnicity

Indicate participant's ethnicity, by marking with a cross (X) in the relevant box.

	White	
1	English/Welsh/Scottish/Northern Irish/British	
2	Irish	
3	Gypsy or Irish traveler	
4	Any other White background, please describe:	
	Mixed/multiple ethnic groups	
5	White and Black Caribbean	
6	White and Black African	
7	White and Asian	
8	Any other Mixed/multiple ethnic background, please describe:	
	Other Ethnic group	
9	Arab	
10	Any other Ethnic group, please describe:	
	Asian/British	
11	Indian	
12	Pakistani	
13	Bangladeshi	
14	Chinese	
15	Any other Asian background, please describe:	
	Black/African/Caribbean/Black British	
16	Black Caribbean	
17	Black African	
18	Black other	
19	Any other Black/African/Caribbean background, please describe:	

Highest qualification

Indicate participant's highest qualification, by marking with a cross (X) in the relevant box.

1	Higher degree	
2	First degree	

3	Other higher qualification	
4	A-level	
5	O-level / GCSE	
6	Other qualification	
7	No qualification	

Marital status

Indicate participant's marital status, by marking with a cross (X) in the relevant box.

1	Married	
2	Single	
3	Partner	
4	Divorced	
5	Widowed	

Occupational status

Indicate participant's occupational status, by marking with a cross (X) in the relevant box.

1	Employed	
2	Self-employed	
3	Voluntary employment	
4	Student / training	
5	House wife / husband	
6	Unemployed	
7	Retired	

Indicate participant's number of hours worked each week, in hours and minutes.

Number of hours worked each week (XX:XX)	

If participant is employed, indicate the participant's occupational group, by marking with a cross (X) in the relevant box.

1	Manager / administrator	
2	Professional (eg, health, teaching, legal)	
3	Clerical worker / secretary	
4	Services / sales	
5	Skilled labour / craftsmen (eg, building, electrical)	
6	Factory worker	
7	Other, please specify:	

Costs

The following questions relate to the various costs associated with participant health care to do with participant health problems. Where the participant is unsure of exact numbers, please ask participant to provide best estimate or average.

Monthly net income

Indicate participant's monthly net income, by marking with a cross (X) in the relevant box.

1	£0.00 - £500.00	
2	£500.00 - £1000.00	
3	£1000.00 +	

Indicate duration of time participant has taken off work because of ill-health in the last 3 months, by indicating numerical values in each box.

1	Months (XX)	
2	Weeks (XX)	
3	Days (XX)	

If participant is unemployed, indicate the primary reason, by marking with a cross (X) in the relevant box.

1	Mental illness	
2	Physical disability	
3	General employment situation	
4	Redundancy	
5	Other, please specify:	

If participant receives social security benefits, indicate by marking with a cross (X) in the relevant box.

	Yes	**No**
Participant receives social security benefits		

If participant does receive social security benefits, indicate which by marking with a cross (X) in the relevant box(es).

1	Income support	
2	Incapacity benefit (pre January 2011 / ESA (post January 2011)	
3	Jobseekers allowance (previously unemployment benefit)	
4	Statutory sick pay	
5	Housing benefit	
6	Severe disablement allowance	
7	Mobility allowance	
8	Family (child tax) credit	
9	Lone parent benefit	

10	Attendance allowance	
11	Other, please specify:	

Indicate participant's total amount of benefit received each week.

Total amount of benefit received per week (£XX.XX)	

Indicate participant's main source of income, by marking with a cross (X) in the relevant box.

1	*Salary / wage*	
2	*State benefits*	
3	*Pension*	
4	*Family support (ie, from spouse)*	
5	*Other, please specify:*	

Use of outpatient hospital services over the last 3 months

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	**No**
Participant has made any outpatient hospital visits in the last 3 months		

If yes, provide further detail below.

	Service	**Total number of appointments in last 3 months**
1	Accident and Emergency department	
2	Radiology department	
3	Physiotherapist	
4	Occupational Therapist	
5	Psychiatric outpatient visit	
6	Other, please specify:	

Use of inpatient hospital services over the last 3 months

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	No
Participant has made any inpatient hospital visits in the last 3 months		

If yes, provide further detail below.

	Service	Total number of admissions in last 3 months	Total number of inpatient days
1	General medical ward		
2	Psychiatric rehabilitation ward		
3	Acute psychiatric ward		
4	Other, please specify:		

Any primary and community care contacts over the last 3 months

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	No
Participant has used any primary and community care services in the last 3 months		

If yes, provide further detail below.

	Service	Total number of contacts in last 3 months	Average duration of each attendance (minutes)
1	GP surgery		
2	GP home visit		
3	Practice nurse		
4	Community psychiatric nurse		
5	Walk-in centre		
6	Out-of-hours care		
7	Occupational therapist		
8	Social worker		

9	Advocate (eg, creative support)		
10	Home-help / home care worker		
11	Community support worker		
12	Psychiatrist		
13	Psychologist		
14	Other, please specify:		

Travel costs

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	**No**
Participant has incurred any travel costs associated with use of services in the last 3 months		

If yes, provide further detail below.

Location	**Main method of travel (eg, private car, bus)**	**Cost of return trip if public transport (£XX.XX)**	**Number of miles round trip if private car (XX.X)**	**Total parking fees (£XX.XX)**
1				
2				
3				
4				
5				
6				

Other costs

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	**No**
Participant has purchased any over-the-counter medicines or attended any private therapy sessions as a result of symptoms during the last 3 months (including herbal or complementary remedies (eg, crystals and visits to alternative practitioners)		

If yes, provide further detail below.

Medicine / preparation / herbal remedy bought or appointment with private practitioner	Total number of purchases or visits in last 3 months	Cost of each remedy or private session
1		
2		
3		
4		
5		
6		
7		

Additional care costs

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	No
Participant has not incurred any additional costs as a result of symptoms such as requiring informal care		

If yes, provide further detail below.

	Type of help	Total number of visits in last 3 months	Average cost of each visit
1	Personal care (eg, washing, dressing, etc)		
2	Help in / around house (eg, cooking, cleaning)		
3	Help outside the home (eg, shopping, transport)		
4	Child care		
5	Other, please specify:		
6	Other, please specify:		

7	Other, please specify:		

Informal care

Indicate yes or no, by marking with a cross (X) in the relevant box.

	Yes	**No**
Participant has someone (other than nurses or home helps), such as a family member, relative, or friend, who provides help (eg, cleaning, cooking, shopping, accompanying to appointments and social events) because of the distress caused by the participant's symptoms		

If yes, provide further detail below.

The relationship of the person to the participant	

	Yes	**No**
Person is in paid employment		

If person is in paid employment, indicate the participant's occupational group, by marking with a cross (X) in the relevant box.

1	Manager / administrator	
2	Professional (eg, health, teaching, legal)	
3	Clerical worker / secretary	
4	Services / sales	
5	Skilled labour / craftsmen (eg, building, electrical)	
6	Factory worker	
7	Other, please specify:	

Indicate persons' number of hours worked each week, in hours and minutes.

Number of hours worked each week (XX:XX)	

Indicate duration of time person has taken off work because of ill-health of the participant in the last 3 months, by indicating numerical values in each box.

1	Months (XX)	
2	Weeks (XX)	
3	Days (XX)	

Indicate the length of time, on average, that the person spends each week looking after / helping the participant, by marking with a cross (X) in the relevant box.

1	1 -5 hours per week	
2	6 – 10 hours per week	
3	11 – 20 hours per week	
4	21 – 35 hours per week	
5	36 – 50 hours per week	
6	50 or more hours per week	
7	Varies: under 20 per week	
8	Varies: more than 20 per week	
9	Other, please specify:	

18 APPENDIX C: EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

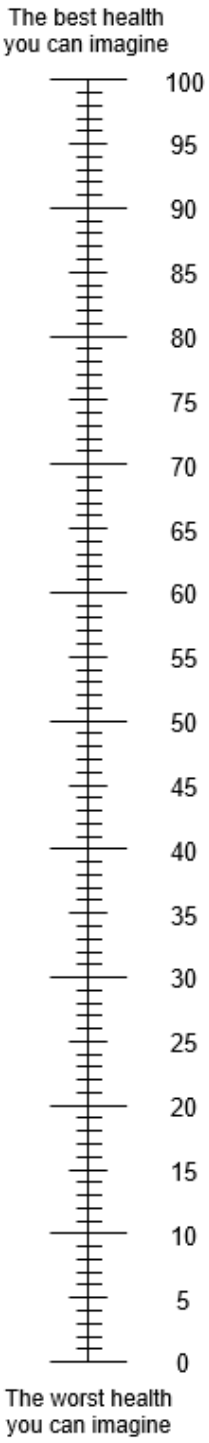
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



19 APPENDIX D: WASA

People's problems sometimes affect their ability to do certain day-to-day tasks in their lives. To rate your problems look at each section and determine on the scale provided how much your problem impairs your ability to carry out the activity.

1. **WORK** - if you are retired or choose not to have a job for reasons unrelated to your problem, please tick N/A (not applicable)

0	1	2	3	4	5	6	7	8	N/A
Not at all		Slightly		Definitely		Markedly	Very severely, I cannot work		☐

2. **HOME MANAGEMENT** – Cleaning, tidying, shopping, cooking, looking after home/children, paying bills etc

0	1	2	3	4	5	6	7	8
Not at all		Slightly		Definitely		Markedly	Very severely	

3. **SOCIAL LEISURE ACTIVITIES -** With other people, e.g. parties, pubs, outings, entertaining etc.

0	1	2	3	4	5	6	7	8
Not at all		Slightly		Definitely		Markedly	Very severely	

4. **PRIVATE LEISURE ACTIVITIES –** Done alone, e.g. reading, gardening, sewing, hobbies, walking etc.

0	1	2	3	4	5	6	7	8
Not at all		Slightly		Definitely		Markedly	Very severely	

5. **FAMILY AND RELATIONSHIPS –** Form and maintain close relationships with others including the people that I live with

0	1	2	3	4	5	6	7	8
Not at all		Slightly		Definitely		Markedly	Very severely	

W&SAS total score

(Data item 39 in the IAPT Data Standard)

20 APPENDIX E: PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems?		Not at all	Several days	More than half the days	Nearly every day
1	Little interest or pleasure in doing things	0	1	2	3
2	Feeling down, depressed, or hopeless	0	1	2	3
3	Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4	Feeling tired or having little energy	0	1	2	3
5	Poor appetite or overeating	0	1	2	3
6	Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7	Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8	Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9	Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

PHQ9 total score ☐

(Data item 37 in the IAPT Data Standard)

21 APPENDIX F: ATHENS INSOMNIA SCALE

1. SLEEP INDUCTION *(time it takes you to fall asleep after turning-off the lights)*

0	1	2	3
No problem	Slightly delayed	Markedly delayed	Very delayed or did not sleep at all

2. AWAKENINGS DURING THE NIGHT

0	1	2	3
No problem	Minor problem	Considerable problem	Serious problem or did not sleep at all

3. FINAL AWAKENING EARLIER THAN DESIRED

0	1	2	3
Not earlier	A little earlier	Markedly earlier	Much earlier or did not sleep at all

4. TOTAL SLEEP DURATION

0	1	2	3
Sufficient	Slightly insufficient	Markedly insufficient	Very insufficient or did not sleep at all

5. OVERALL QUALITY OF SLEEP *(no matter how long you slept)*

0	1	2	3
Satisfactory	Slightly unsatisfactory	Markedly unsatisfactory	Very unsatisfactory or did not sleep at all

6. SENSE OF WELL-BEING DURING THE DAY

0	1	2	3
Normal	Slightly decreased	Markedly decreased	Very decreased

7. FUNCTIONING (PHYSICAL AND MENTAL) DURING THE DAY

0	1	2	3
Normal	Slightly decreased	Markedly decreased	Very decreased

8. SLEEPINESS DURING THE DAY

0	1	2	3
None	Mild	Considerable	Intense

22 APPENDIX G: ANXIETY LOG BOOK

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

Date	Current setting		Length of treatment (minutes)	
	Time of score (before treatment)		Anxiety score	
	Time of score (after treatment)		Anxiety score	

23 APPENDIX H: CE MARK

EC Certificate Full Quality Assurance System: Certificate US98/13201

The management system of

Electromedical Products International, Inc.

2201 Garrett Morris Parkway,
Mineral Wells, TX, 76067, United States

has been assessed and certified as meeting the requirements of

Directive 93/42/EEC

on medical devices, Annex II (excluding Section 4)

For the following products

Cranial electrotherapy stimulation devices for the treatment of anxiety disorders of all levels of severity, mild depression accompanying anxiety and insomnia associated with anxiety and pain.

Where the above scope includes class III medical device(s), a valid EC Design Examination Certificate according to Annex II (Section 4) is a mandatory requirement for each device in addition to this certificate to place that device on the market.

This certificate is valid from 12 April 2016 until 12 September 2020
and remains valid subject to satisfactory surveillance audits.
Re certification audit due before 12 September 2018
Issue 9. Certified since 11 May 1998

Certification is based on reports numbered WWMW 07692

Authorised by

SGS United Kingdom Ltd, Notified Body 0120
202B Worle Parkway, Weston-super-Mare, BS22 6WA UK
t +44 (0)1934 522917 f +44 (0)1934 522137 www.sgs.com

SGS CE 02 0215

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24 APPENDIX A: INSURANCE CERTIFICATE

ACORD

CERTIFICATE OF LIABILITY INSURANCE

DATE (MM/DD/YYYY): 1/18/2016

THIS CERTIFICATE IS ISSUED AS A MATTER OF INFORMATION ONLY AND CONFERS NO RIGHTS UPON THE CERTIFICATE HOLDER. THIS CERTIFICATE DOES NOT AFFIRMATIVELY OR NEGATIVELY AMEND, EXTEND OR ALTER THE COVERAGE AFFORDED BY THE POLICIES BELOW. THIS CERTIFICATE OF INSURANCE DOES NOT CONSTITUTE A CONTRACT BETWEEN THE ISSUING INSURER(S), AUTHORIZED REPRESENTATIVE OR PRODUCER, AND THE CERTIFICATE HOLDER.

IMPORTANT: If the certificate holder is an ADDITIONAL INSURED, the policy(ies) must be endorsed. If SUBROGATION IS WAIVED, subject to the terms and conditions of the policy, certain policies may require an endorsement. A statement on this certificate does not confer rights to the certificate holder in lieu of such endorsement(s).

PRODUCER	CONTACT NAME: Becky Essner, ACSR, PIWT
Higginbotham Insurance Agency, Inc. 500 W. 13th Street Fort Worth TX 76102	PHONE (A/C, No, Ext): 800-728-2374 FAX (A/C, No): 817-347-6981 E-MAIL ADDRESS: bessner@higginbotham.net

INSURER(S) AFFORDING COVERAGE	NAIC #
INSURER A : Federal Insurance Company	20281
INSURER B :	
INSURER C :	
INSURER D :	
INSURER E :	
INSURER F :	

INSURED: Electromedical Products Intl, Inc.
2201 Garrett Morris Parkway
Mineral Wells TX 76067

COVERAGES **CERTIFICATE NUMBER:** 672501760 **REVISION NUMBER:**

THIS IS TO CERTIFY THAT THE POLICIES OF INSURANCE LISTED BELOW HAVE BEEN ISSUED TO THE INSURED NAMED ABOVE FOR THE POLICY PERIOD INDICATED. NOTWITHSTANDING ANY REQUIREMENT, TERM OR CONDITION OF ANY CONTRACT OR OTHER DOCUMENT WITH RESPECT TO WHICH THIS CERTIFICATE MAY BE ISSUED OR MAY PERTAIN, THE INSURANCE AFFORDED BY THE POLICIES DESCRIBED HEREIN IS SUBJECT TO ALL THE TERMS, EXCLUSIONS AND CONDITIONS OF SUCH POLICIES. LIMITS SHOWN MAY HAVE BEEN REDUCED BY PAID CLAIMS.

INSR LTR	TYPE OF INSURANCE	ADDL INSD	SUBR WVD	POLICY NUMBER	POLICY EFF (MM/DD/YYYY)	POLICY EXP (MM/DD/YYYY)	LIMITS	
A	X COMMERCIAL GENERAL LIABILITY			35858200	1/18/2016	1/18/2017	EACH OCCURRENCE	$1,000,000
	CLAIMS-MADE X OCCUR						DAMAGE TO RENTED PREMISES (Ea occurrence)	$1,000,000
							MED EXP (Any one person)	$10,000
							PERSONAL & ADV INJURY	$1,000,000
	GEN'L AGGREGATE LIMIT APPLIES PER:						GENERAL AGGREGATE	$2,000,000
	X POLICY PRO-JECT LOC						PRODUCTS - COMP/OP AGG	$
	OTHER:							$
	AUTOMOBILE LIABILITY						COMBINED SINGLE LIMIT (Ea accident)	$
	ANY AUTO						BODILY INJURY (Per person)	$
	ALL OWNED AUTOS / SCHEDULED AUTOS						BODILY INJURY (Per accident)	$
	HIRED AUTOS / NON-OWNED AUTOS						PROPERTY DAMAGE (Per accident)	$
								$
	UMBRELLA LIAB OCCUR						EACH OCCURRENCE	$
	EXCESS LIAB CLAIMS-MADE						AGGREGATE	$
	DED RETENTION $							$
	WORKERS COMPENSATION AND EMPLOYERS' LIABILITY Y / N						PER STATUTE / OTH-ER	
	ANY PROPRIETOR/PARTNER/EXECUTIVE OFFICER/MEMBER EXCLUDED? N / A (Mandatory in NH)						E.L. EACH ACCIDENT	$
	If yes, describe under DESCRIPTION OF OPERATIONS below						E.L. DISEASE - EA EMPLOYEE	$
							E.L. DISEASE - POLICY LIMIT	$
A	Products Liability Claims Made Form			99470671	1/18/2016	1/18/2017	See Below	

DESCRIPTION OF OPERATIONS / LOCATIONS / VEHICLES (ACORD 101, Additional Remarks Schedule, may be attached if more space is required)

Products Liability: Products & Completed Operations Aggregate: $2,000,000
Each Occurrence: $2,000,000
Claims Made Deductible: $10,000

Medical Devices

See Attached...

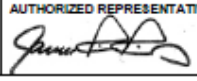
CERTIFICATE HOLDER

Electromedical Products Intl, Inc.
For Information Purposes Only
not to be altered
- - -

CANCELLATION

SHOULD ANY OF THE ABOVE DESCRIBED POLICIES BE CANCELLED BEFORE THE EXPIRATION DATE THEREOF, NOTICE WILL BE DELIVERED IN ACCORDANCE WITH THE POLICY PROVISIONS.

AUTHORIZED REPRESENTATIVE



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