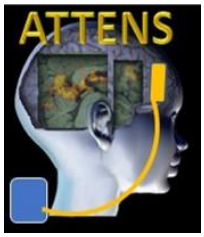
1. PROTOCOL/CLINICAL INVESTIGATION PLAN FULL TITLE

A multi-centre, double-blind, randomized, parallel-group, phase IIb study to compare the efficacy of real versus sham external Trigeminal Nerve Stimulation (eTNS) on symptoms in youth with Attention-Deficit/Hyperactivity Disorder (ADHD)

Protocol Short Title/ Acronym: ADHD trial of external trigeminal nerve stimulation (ATTENS)



Trial Identifiers

ISRCTN:	ISRCTN82129325		
REC Number:	IRAS: 299703		
UKCRN Number:			
Protocol Version Number:	4.0	Date:	31/03/2022

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2.Study Synopsis

TITLE OF CLINICAL TRIAL:	A multi-centre, double-blind, parallel-group, randomized controlled study to compare the efficacy of real versus sham external Trigeminal Nerve Stimulation (eTNS) on symptoms in youth with Attention Deficit/Hyperactivity Disorder (ADHD)
Protocol Short Title/ Acronym:	ATTENS
Study Phase If Not Mentioned In Title:	Phase IIb
Sponsor Name:	Joint King's College London; South London and Maudsley NHS Foundation Trust
Chief Investigator:	Prof Katya Rubia
UKCRN Number:	
REC Number:	21/WM/0169
Medical Condition Or Disease Under Investigation:	Attention-Deficit/Hyperactivity Disorder (ADHD)
Purpose Of Clinical Trial:	To determine if eTNS treatment significantly reduces symptoms of ADHD.
Primary Objective:	To examine whether 4 weeks of nightly administration of real versus sham eTNS in ADHD children will significantly improve weekly investigator-assessed parent ratings of the ADHD-RS
Secondary Objective(s):	To evaluate whether short term (up to 4 weeks) of nocturnal real eTNS versus sham eTNS will: 1. Improve other measures of ADHD core symptoms: a) Teacher and parent-rated Conners ADHD symptoms b) Teacher-rated severity of ADHD (ADHD-RS)c) Child-rated Strength and Difficulties Questionnaire (SDQ) 2. Improve ADHD-related problems such as: a) Daily life executive functioning rated by parents and children b) Emotional dysregulation rated by parents and children c) Mind-wandering rated by children d) Depression and anxiety rated by parents and children 3. Improve cognitive performance in a range of executive functions including attention, inhibition, switching and timing 4. Measures of the Columba Suicide Severity Rating Scale 5. Show sustained effects at 6 months 6. Have a good safety profile

	7. Affect the sleep patterns of children with ADHD rated by parents 8. Improve physiological measures a) Heart rate; heart rate variability and objective hyperactivity measures tested in a wrist-hand device b) Pupil diameter and head movement measured during rest and one of the cognitive tasks. **Mechanistic secondary objectives:** Assess the mechanisms of action of eTNS on brain activation in ADHD children between 10- and 18-years using fMRI during 3 tasks and a resting state measured at pre and post-treatme timepoints.
Trial Design:	Confirmatory, Phase IIb, parallel-group, sham-controlled, double-blind (participant, parent, assessor, researchers and analysts), superiority, multicentre RCT
Endpoints:	Parent ratings of the ADHD-RS (primary outcome), measured at baseline and weekly during treatment and at 6 months follow-up All outcome measures listed under secondary objectives.
Sample Size:	150 children and adolescents with ADHD
Summary Of Eligibility Criteria:	Children and adolescents with a clinical diagnosis of ADHD based on the DSM-5 criteria (K-SADS). 1) Severity of ADHD above 24 on the ADHD-Rating Scale (ADHD-RS); scoring above clinical cut-off for ADHD on the Schedule for Affective Disorders and Schizophrenia, ADHD module (K-SADS); scoring above clinical cut-off for ADHD on the short forms of the Conners Parent Rating Scales (Conners 3 P-S) 2) IQ > 70 3) Medication: can either be medication-naïve, not currently on medication, or come off their stimulant medication for 2 weeks before the trial and during the 4 weeks treatment or be on stable stimulant medication for trial duration.
Intervention (Description, frequency, details of delivery)	Participants will undergo four weeks of 8 hours eTNS every night administered by the parents (or themselves if they have capacity). The eTNS device will send stimulation 30s on and 30s off when in use ranging from 0-10mA.
Comparator Intervention:	Sham eTNS. The sham eTNS device will send stimulation at a low frequency for 60s at the start of every hour when in use
Maximum Duration Of Treatment Of A Subject:	4 weeks of 8 hours real or sham eTNS nightly
Version And Date Of Final Protocol:	4.0 31.03.22
FVersion And Date Of Protocol Amendments:	v.2.0 14.08.21 v.3.0 09.02.22

3. Revision History

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date
v.2.0 14.08.21	First approved protocol	20.09.21

v.3.0 09.02.2022	1) Change to a clinical investigation of a non-UKCA/CE marked device for use where commercialization is intended which leads to MHRA approval needed (although we do not intend to commercialise the device, but MHRA is needed to purchase the devices) 2) No longer able to offer all participants the use of the real device for four weeks at the end of the trial 3) Corrections and clarifications of the Trial Flow chart section 7.3 4) Removal of the American Psychiatric Association Diagnostic and Statistical Manual (DSM-5) ADHD criteria (already in K-SADS), adverse events questionnaire (recorded freely in AE recording), and the working memory task for the neurocognitive tasks. Also, removal of the locus coeruleus scan for those doing the fMRI. 5) Clarification and justification of eligibility criteria and participants no longer need to be off medication for 24-36 hours prior to research assessment and if participants are on stimulant medication they need to remain on stable dose and not take any "drug holidays". In addition, participants with dermatitis and those who are currently receiving any other non-medical treatment will be excluded. 6) The sham device will provide stimulation for 60s rather than 30s at a low frequency 7) Data management section updated regarding fMRI. The data from E4 Empatica wristband and Tobii pro eye tracker will be pseudoanonymised (dummy information) and then entered onto these platforms. 8) The term "gender" has been changed to "sex" to refer to a person's physical characteristics rather than a person's identity 9) Clarifying that this is a superiority trial in the title and in 7.1. Trial Objectives and 7.2. Trial Design. 10) Justification for the duration of treatment (7.2) 11) Section added regarding changes to the trial in case of a pandemic or natural disaster (end of Section 7) 12) Section added regarding labeling of the devices "exclusively for clinical investigations" in 8.1.1. 13) Section 8.7. added regarding risks and burdens to the participants 14) Added that all protocol deviations are being reported to the DMC and those deemed important reported to MHRA (Section 11.6) 15) Clarifications regarding safety reporting and added that it is sponsor responsibility to report to MHRA (Section 10.5) 16) Sections regarding ethical and regulatory approvals that needed to be updated to include REC committee details and MHRA (Section 18) 17) SPIRIT Statement added (Section 19)	

	18) Financial aspect section updated to add any conflict of interest (CoI) for Chief Investigator and the co-applicants (section 24. Financial Aspects) 19) Data sharing statement moved to a separate section rather than being included in the confidentiality agreement (Section 26). 20) Start and anticipated end date for the project (Section 10.7.) 21). Adding the Columbia Suicide Severity Rating Scale (sections 7.3, 11.5, 11.8, 11.9, 12.2, 12.3, 12.6) and acceptability survey 22) Correction of definition of treatment response according to NICE guideline that reduction is 20% rather than 25% on the ADHD-RS measure (Section 14.3) 23) Clarification regarding side effect (section 13) 24) The child-rated Strength and Difficulties Questionnaire (SDQ) has been added after request from MHRA 25) Clarification regarding the reporting by the junior statistician to the DMC in relation to treatment arm and unblinded information (section 11.3 and 16). 26) Clarification regarding the statistical analysis as requested by MHRA (section 14.3)	
v.4.0 31.03.22	1) Section 13,2 clarification regarding adverse event reporting 2) Section 12.2 Secondary Efficacy Parameters: clarification regarding physiological measures	

4. Glossary of terms (Optional)

ADHD = Attention-Deficit/Hyperactivity Disorder

ADHD-RS = ADHD rating scale

ARI = Irritability scale.

BRIEF-2 = the Behaviour Executive Function Questionnaire-Self-report measure second edition

Conners 3 S P/T-S = Short forms of the Conners Parent and Teacher Rating Scales.

C-SSRS= Columbia- Suicide Severity Rating Scale

DMC= Data Monitoring Committee

eTNS = external Trigeminal nerve stimulation

fMRI= functional magnetic resonance imaging

IOPPN = Institute of Psychiatry, Psychology & Neuroscience

KCL = King's College London.

KSADS: Schedule for Affective Disorders and Schizophrenia, ADHD module (K-SADS)

MEWS: The mind excessive wandering scale; a mind-wandering questionnaire rated by children

RCADS-25 and RCADS-25-P; Revised Child and Adolescent Depression scale short form child and parent rated

SAP = Statistical Analysis Plan

SDSC = Sleep Disturbance Scale for Children (parent rated)

SDQ: Strength and Difficulties Questionnaire (SDQ)

TMG = Trial Management Group

TSC = Trial Steering Group

5. Protocol Contents

6. BACKGROUND RATIONALE AND DESIGN

Attention-deficit/hyperactivity disorder (ADHD) affects around 7% of children and is characterised by age-inappropriate and impairing symptoms of inattention and/or impulsiveness/hyperactivity. Symptoms persist into adulthood in most cases it is associated with worse academic and social outcomes. Children with ADHD commonly have impairments in one or more executive functions, most prominently in sustained attention, working memory, and inhibitory control and in the function of the mediating fronto-striatal and fronto-parietal networks (Rubia, 2018). Stimulant medication is the prevalent treatment but is not preferred due to commonly occurring side effects, is not suitable for all patients, and compliance is poor in adolescence. Alternative non-medication treatments with less side effects are desirable but have so far only shown modest effects. External Trigeminal nerve stimulation (eTNS) is the first non-pharmacological ADHD treatment approved in 2019 by the USA Food and Drug administration (FDA), although efficacy/safety data do not exist beyond a pilot study on 62 subjects and mechanisms of action are not understood. eTNS is a minimal risk, non-invasive neuromodulation that sends low electrical pulses under the skin on the forehead targeting the trigeminal system and can be applied during sleep. Small electrical currents are transmitted transcutaneously via a self-adhesive, supraorbital electrode to excite (trigger action potentials) on the supratrochlear and supraorbital branches of the ophthalmic nerve (V1) located under the skin of the forehead. The supraorbital nerve is a branch of the first trigeminal division . The trigeminal nerve has widespread connections to the brain, in particular the reticular activation system, locus coeruleus (LC), brain stem, thalamic, frontal and cortical areas, as well as effects on dopamine and noradrenaline, all of which have effects on arousal and attention (Aston-Jones and Cohen, 2005) and been implicated in ADHD (Rubia, 2018). A proof-of-concept pilot randomised controlled trial (RCT) in 62 children with ADHD showed improvement of ADHD symptoms after 4 weeks of real compared to sham eTNS administered every night for 8 hours by parents, with minimal side effects and no serious adverse effects (McGough et al., 2019). An open trial of eTNS of 6 weeks in children with ADHD showed additional improvements of executive functions concomitant with clinical improvement (McGough et al., 2015).

Based on evidence from this small, underpowered pilot study, eTNS is now FDA approved for ADHD. More evidence is clearly needed to demonstrate the efficacy and effectiveness of eTNS for reducing ADHD symptoms and to understand its currently unknown underlying mechanisms of action. We therefore plan to conduct a well powered confirmatory, randomised sham controlled RCT of eTNS across two sites, London and Southampton, with recruitment across 3 cities (London, Southampton and Portsmouth) over 4 weeks in 150 children with ADHD to establish/confirm whether eTNS is efficacious in improving ADHD symptoms and cognitive functions and to test potential longer-term effects. We will measure the same primary and secondary clinical outcome measures as the USA trial as well as additional ADHD-relevant clinical measures such as mind-wandering, which is a key feature of ADHD, and sleep quality. Furthermore, we will assess a wider range of ADHD-relevant executive functions than the previous trials (which only measured attention and working memory) to more thoroughly assess effects of eTNS on cognition, including measures of motor and interference inhibition, sustained attention, vigilance, and timing and will hence be more conclusive with respect to cognitive improvement effects. Also, the previous trial used EEG to understand the underlying mechanisms of action which has poor spatial resolution and is not ideal for a treatment that works subcortically via the brain stem and other subcortical regions which cannot be assessed with EEG. This RCT will for the first time address the question of the underlying mechanism of action of eTNS on the brain of children/adolescents with ADHD by use of fMRI, which can measure deep subcortical brain regions with high spatial resolution. The trial will be able to test ***how*** and ***why*** eTNS works (if it does) on the ADHD brain by showing which brain deficits will be improved or normalised with the treatment. Last, this study has the power to explore treatment predictors including clinical, cognitive and physiological measures such as heart rate and pupil diameter and may be able to identify a subgroup of patients who respond optimally to the treatment, perhaps by easy-to-measure indicators such as heart rate or pupil diameter which is an indicator of LC activity/arousal, and which would be highly clinically useful for precision medicine.

The study will confirm whether eTNS is an effective non-drug treatment for ADHD behaviour that has minimal side effects and can be administered in-house and hence is likely to be preferred by patients, parents, and clinicians. Such a treatment would improve the healthcare and disease burden for patients.

7. TRIAL OBJECTIVES AND DESIGN

7.1. TRIAL OBJECTIVES

To conduct a confirmatory, sham-controlled, parallel-arm, double-blind (participant, parent, researcherand analyst), phase IIb, multicentre superiority RCT to further establish in a large group of 150 children and adolescents with ADHD whether eTNS over 4 weeks improves ADHD symptoms (main outcome measure) and other ADHD-related symptoms and behaviours, executive function performance on a task battery of tasks of inhibition, switching, attention, vigilance and time estimation , whether it improves sleep, whether it has an effect

on physiological measures, and whether effects on primary and secondary outcome measures persist at 6 month follow-up, whether we can establish predictors of treatment efficacy and to understand the underlying mechanism of action on ADHD brain function.

7.1.1. Primary Objective

To examine whether 4 weeks of nightly administration of real versus sham eTNS in ADHD children will improve weekly investigator-assessed parent ratings of the ADHD-RS.

7.1.2. Secondary objectives

To evaluate whether short term (4 weeks) of nocturnal real eTNS versus sham eTNS will:1. Improve other measures of ADHD core symptoms measured at baseline, weekly during the 4-week trial and at 6 months after randomisation, i.e. the parent-rated ADHD symptom severity as measured in the short forms of the Conners Parent Rating Scale (Conners 3 P-S) (Conners et al., 2008, 2011), and the child-rated Strength and Difficulties Questionnaire (SDQ) (Goodman et al., 1998).

2**.** Improve other measures of ADHD core symptoms and related measures, measured at baseline, after 4 weeks and at 6 months after randomisation:

a. Teacher-rated severity of ADHD symptoms as assessed by the Conners Teacher Rating Scale (Conners 3 T-S) (Conners 2008,Conners et al.,2011) and the teacher rated ADHD-RS.
b. Emotional dysregulation, measured in the parent and child rated Irritability questionnaire (ARI) (Stringaris et al., 2012)
c. The degree of mind-wandering as assessed by the self-rated Mind Excessive Wandering Questionnaire (MEWS) (Mowlem et al., 2019).
d. Ratings of depression and anxiety using the revised child and adolescent depression scale rated by children and by parents (RCADS-25 and RCADS 25-P (Ebesutani et al., 2017; Ebesutani et al., 2012)
e. Ratings on the Columbia Suicide Severity Scale (Posner et al., 2011).
f. Daily Life Executive Function Behaviour, using the Behaviour Executive Function Questionnaire-Self-report measure (BRIEF-2) and the Behaviour Executive Function Questionnaire-parent-report measure (BRIEF-2))(Gioia et al., 2000).
g. Cognitive performance in a range of executive functions including attention, inhibition, switching, and timing

3. Show sustained effects at 6 months in all primary and secondary outcome measures

4. Have a good safety profile measured weekly during the trial and at follow-up in questionnaires of side effects adapted to eTNS rated by children and parents (McGough et al., 2019) (5min) and adverse events recording in the adverse events log.

5. Affect the sleep patterns of children with ADHD rated by parents using the parent-reported Sleep Disturbance Scale for Children (SDSC) (Bruni et al., 1996).

6. Improve physiological measures,

a) Heart rate; heart rate variability and objective hyperactivity measures tested in a wrist-hand device measured at baseline and post-treatment.

b) Pupil diameter and head movement measured during rest and one of the cognitive tasks measured at baseline and post-treatment and at follow-up.

7. Mechanistic objective:

To assess the mechanisms of action of eTNS on brain activation in ADHD children between 10- and 18-years using fMRI during 3 tasks and a resting state measured at pre and post treatment timepoints.

7.2. TRIAL DESIGN

UK, multicentre, phase IIb, double-blind (participant, parent, researcher and analyst), parallel group, sham-controlled, superiority randomised controlled trial.

The study will be conducted across 2 centres to increase representativeness and higher rates of participant enrolment. The treatment duration will be 4 weeks as this has shown to be the optimal time period to elicit changes in ADHD symptoms in the pilot and pivotal studies (McGough et al., 2015, 2019). This is based on findings from the open 8-week trial where clinical changes were apparent in the first 4 weeks to avoid drop-outs in longer sham-controlled trials. A follow-up period of 6 months was chosen as this is standard for longer-term effects in studies of neurotherapies (and drugs) in ADHD (Alegria et al., 2017, Westwood et al., 2021).

7.3. TRIAL FLOWCHART

	Eligibility At home and at the research centre	Baseline measure at home or at the research centre (if participant is doing the fMRI it needs to be at the research centre twice). This may be split between two visits.	After randomisation	eTNS 1st week	eTNS 2nd week	eTNS 3rd week	eTNS 4th week/ Endpoint at research centre*	6-month after randomisation Follow-up at research centre+
Consent form child (2 min)	x	x						
Consent form parent (2 min)	x	x						
Eligibility checklist (10 min)	x							
Background information (10 min)	x							
Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (1-1.30 hr) (P)	x							
Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) (50 min) (C)	x							
ADHD Rating Scale (ADHD-RS) (P) (10min)	x[1]	x[1]		x	x	x	x	x
Conners Parent Rating Scale (Conners 3 P-S) (10 min)	x[1]	x[1]		X	X	X	X	x
Verbal tests of WASI-II (20 min)	x							
Medication form (P or C) (5 min)	x							
Non-verbal tests of WASI-II (20 min)	x							
ADHD Rating Scale (ADHD-RS) (T) (5-10min)		x					x	

Conners' Teacher Rating Scale (Conners 3 T--S) (T) (5-10min)		x					x	
Strength and Difficulties Questionnaire (SDQ) (C) (10min)		X					X	X
Edinburgh Handedness (C) (5min)		x						
Behaviour Rating Inventory of Executive Function (BRIEF-2) (C) (15 min)		x					x	x
Behaviour Rating Inventory of Executive Function (BRIEF-2) (P) (15 min)		x					x	x
Columbia Suicide Severity Rating Scale (C-SSRS) (Child) (2 min)		x					x	x
Affective Reactivity Index self-rating (ARI-S) (C) (2min)		x					x	x
Affective Reactivity Index self-rating (ARI-P) (P) (2min)		x					x	x
Mind Excessively Wandering Scale (MEWS) (C) (5min)		x					x	x
Revised Children's Anxiety and Depression Scale (RCADS-25) (P) (15 min)		x					x	x
Revised Children's Anxiety and Depression Scale (RCADS-25) (C) (15 min)		x					x	x
Sleep disturbance Scale for Children (SDSC) (P) (10min)		x					x	x
Sleep diary (2min)				x	x	x	x	
Blinding Questionnaire parents (2min)				x			x	
Blinding Questionnaire children (2min)				x			x	
Blinding Questionnaire researcher (2min)				x			x	
Acceptability survey (P) (C) (2 min)							x	
	Device training							
Parents trained in device use (15 min)			x					
Use of device				x	x	x	x	
Trial Manager to check device use with family during week 1				x				
	Safety measures							
Side effects (2min) (C, P)		x		x	x	x	x	
Adverse events log (2min) (C, P)				x	x	x	x	
Concomitant medication log		x		x	x	x	x	x
	Lab measures for monitoring							

Height, weight and vital signs (10 min)		x					x	x
	Neurocognitive measures							
Go-no go task (5min)		x					x	x
Continuous performance task (8min)		x					x	x
Interference inhibition (Simon Task) (5min)		x					x	x
Time estimation task (5 min)		x					x	x
Vigilance task (5min)		x					x	x
	Physiological measures							
Objective measure of heart rate, its variability and hyperactivity measure (wrist-held electronic device) to be used for 24 hours prior to research visit		x					x	
Pupil diameter and head motion during rest and tasks		x					x	x
	fMRI measures in subgroup of 56 patients							
Mock scan (can only take place at the research centre)		x						
fMRI safety form (5 min)		x					x	
fMRI request form (10 min)		x						
Stop task (6 min)		x					x	
Sustained Attention task (12min)		x					x	
Working memory task (5 min)		x					x	
Resting state fMRI (10min)		x					x	
	Forms							
Receipt of payment (1 min)		x					x	x

[1] This will only be obtained once if the eligibility and baseline visit is within three weeks. If longer than three weeks the measure will be obtained again

* testing window of +7 days

+ testing window of +-6 weeks

In case of a global or regional pandemic or natural disaster there may have to be some changes to the measures that can be collected. If no face-to-face contact can be had, the study will not be able to do the fMRI aspects of the study, the neurocognitive measures, the pupil measures, or the measurement of vital signs. However, all other data including the primary and the most important secondary outcome measures can be obtained online and the study would not lose its primary value.

8. TRIAL INTERVENTION

8.1. THERAPY/INTERVENTION DETAILS

Real eTNS group

eTNS will be performed with the Monarch eTNS System (NeuroSigma, Inc, Los Angeles, CA). The Monarch eTNS system received the European CE Mark in 2012 for epilepsy and depression and in October 2015 for ADHD and FDA clearance in April 2019 as a medical device for the treatment of patients with ADHD. The European CE mark was not renewed in August 2021.This was a business decision due to the development of the next-generation version of the

Monarch eTNS device and not related to any safety and efficacy issues. The next-generation device will deliver the exact same stimulation parameters as the current generation product (but will be smaller and have a better user interface) and thus the clinical findings from this study will still be relevant. The Medicine and Healthcare products Regulatory Agency (MHRA) confirmed that given the change of the Monarch eTNS device from a CE marked device to a non-CE/ UKCA device the study now requires MHRA approval and this falls under the category of a clinical investigation of a medical device. The procedures for eTNS are based on well validated and safe methods used in the previous work in ADHD (McGough et al., 2015; McGough et al., 2019) as well as in other disorders such as adult depression, epilepsy and post-traumatic stress disorder (Cook et al., 2016). The stimulator is worn on the subjects' pyjama/T-shirt and attached with thin wires to disposable, silver-gel, self-adhesive patch electrodes. Parents or the older adolescent will apply a disposable patch across their child's forehead to provide bilateral stimulation for ~8 hours during sleep. The active condition will use 120Hz repetition frequency with a 250ms width, and a duty cycle of 30s on and 30s off. Stimulator settings will be established at baseline by titration in 0.2 mA increments ranging from 0 to 10mA , which will identity a stimulation level which is perceptible but below the participants' subjective level of pain/discomfort. Each night, parents will turn on the device and press the up button to the maximum tolerable stimulation mA that is perceptible but not painful or uncomfortable or until the device reached the maximum current (depending on the patient). In the active condition, the current that flows to the patch is limited to a safe range (maximum 10mA). Once the optimal stimulation level is established for each patient, it will be turned on for 8 hours during the night and will be 30s on and 30s off throughout.

Sham eTNS group

It is common practice in brain stimulation studies to use sham stimulation as control condition (Antal et al., 2017, Rubia et a. 2021). The placebo effect is particularly pronounced in studies that use technology and hence need to be controlled for (Antal et al., 2017). Subjects randomized to the sham group will receive a Monarch eTNS system identical in appearance and graphical user interface to the active stimulation device, but with the electrical stimulation routed through an internal resistor instead of the adhesive electrical patch after the first 60s. This ensures that the rechargeable battery still drains appropriately and requires the subject to recharge it after each nightly therapy session, to maintain the study blind (see also McGough et al. 2015, 2019). Participants are informed at a scripted presentation that "pulses may come so fast or so slowly that the nerves in the forehead might or might not detect a sensation". They are also told that most people do not feel the stimulation any more after some time (which is true). Like in the real eTNS condition, each night, parents (or older teenagers) will turn on the device and press the up button until the stimulation is perceptible but not uncomfortable or painful or until the device reaches the maximum current (depending on the patient). With sham, current will flow for 60s every hour at a low frequency (Shiozawa et al. 2015) and then be routed through the internal resistor. The scalp quickly adapts to stimulation and patients will not notice whether they receive the real or sham device (Shiozawa et al., 2015) .

eTNS is very simple to apply. The NeuroSigma company that develops the device will provide training at the beginning of the trial and train the RAs & trial managers in the application of the device. In addition, instruction videos and a manual will be used to train parents in the device application. Collaborator Dr Abdelghani who has been using the device routinely in his ADHD clinic will also assist with the training of the administration of the device.

8.1.1 Labelling the devices

All the devices will be labelled "exclusively for clinical investigations" as per MHRA guidelines.

8.2. FREQUENCY AND DURATION OF INTERVENTION

The intervention will be applied every night for 8 hours over 4 weeks.

Participants will be tested for eligibility, pre-assessed, then receive the intervention for 4 weeks which they will apply themselves at home, receive a post-assessment a few days (+7 days) after treatment end, and will be assessed at follow-up at 6 months after randomisation (+- 6 weeks). The duration of the intervention is 4 weeks. The total length of participant participation in the trial (including eligibility, pre- and post-assessments, and follow-up assessments) is therefore about 6 months and a few days/weeks.

8.3. INTERVENTION RECORDS

Participants will be asked to keep a sleep diary recording the number of hours they had the eTNS applied during each night during the 4 weeks.

8.4. SUBJECT COMPLIANCE

Compliance with the treatment protocol is assessed at each weekly visit by reviewing the sleep diaries that caregivers (or young people with capacity and who prefer to do it themselves) filled out each day indicating for how many hours and the level of stimulation they used the device each night.

8.5 STUDY ADHERENCE

We will ask participants to record adherence to the study and to record the length of time eTNS was applied each night in a daily sleep diary. We will emphasize adherence and the importance to honestly report usage of the device.

Adherence will be defined in the Statistical Analysis Plan.

Use of the eTNS treatment will be recorded in the sleep diary.

8.6. CONCOMITANT MEDICATION

Concurrent stimulant medication is allowed as long as it is stable regimen.

Patients who take atomoxetine or guanfacine will not be included in the trial since these medications may affect the activity of the locus coeruleus and pupil dilatation. Participants will not be allowed to take part in other medical or other treatments that can change their ADHD symptoms during the trial.

8.7. RISKS AND BURDENS TO THE PARTICIPANTS

Possible discomfort: it could potentially be a bit uncomfortable to sleep with the eTNS device at night. However, the previous studies found that sleep was improved with eTNS (McGough et al., 2015, 2019).

Potential delay of medication treatment: no changes to medication treatment should be done during the four weeks of research treatment hence potential participants would have to either delay start of medication treatment or participation in the trial.

Personal information in the assessments: some of the questions seem personal and can cause distress but these are similar to those asked during a mental health assessment.

Side effects: no serious side effect or adverse events have been reported in studies with eTNS and we do not expect any serious side effects. See Section 13 on safety. The most common side effects are headaches and skin irritation which are temporary and go away without treatment.

Contraindications to eTNS are listed under the exclusion criteria (i.e., implanted cardiac or neurostimulation systems, implanted metallic or electronic device in their head; presence of body worn devices (e.g., insulin pumps and t-VNS) or dermatitis.

9. Research environment

The study will be conducted at two academic institutions, the Department of Child & Adolescent Psychiatry/Social Genetic and Developmental Psychiatric Centre (SGDP), Institute of Psychiatry, Psychology and Neuroscience, at King's College London, UK, and the Centre for Innovation in Mental Health (CIMH), School of Psychology, University of Southampton, UK.

All fMRI scans will be completed at the 3T GE scanner at the Centre for Neuroimaging Sciences (CNS) at the Institute of Psychiatry, Psychology and Neuroscience, King's College London.

10. SELECTION AND WITHDRAWAL OF SUBJECTS

10.1. INCLUSION CRITERIA

1) Children and adolescents, aged 8-18 years at study entry
2) ADHD diagnosis (DSM-5)
3) A score higher than 24 on the investigator-scored parent-rated ADHD-RS (DMS-5) (to include participants who still have relatively high symptoms)
4) Scoring above clinical cut-off for ADHD (5 or above) on the parent Kiddie Schedule for Affective Disorders and Schizophrenia, for School-age Children- present and lifetime version, ADHD module (K-SADS) (Kaufman et al., 1996)
5) Scoring above clinical cut-off (i.e., > 60) for ADHD on the short forms of the Conners Parent Rating Scales (Conners 3 P-S)(Conners et al.,2011, Conners, 2008)
6) IQ above 70 as assessed on the Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler, 1999) (to exclude participants with learning disability)
7) Patients should be either medication-naïve, OR willing to come off their stimulant medication for one week before the trial OR willing to be on stable medication for the duration of the trial.

10.2. EXCLUSION CRITERIA

1) Comorbidity with any other major psychiatric disorder (expect conduct/oppositional defiant disorder, mild

anxiety and depression- as assessed on the K-SADS, as these are commonly associated with ADHD)

2) Alcohol and substance abuse (as assessed on the K-SADS) (potential confound)

3) Neurological abnormalities, such as epilepsy (potential confound)

4) Current medication with atomoxetine or guanfacine or in the past two weeks (as these have an effect on the arousal system to be improved with eTNS)

5) Participants who usually take drug holidays on weekends or holidays will not be able to participate in the study unless they are willing to take their stimulant medication in a stable way throughout the study or not at all throughout the study and 1 week before the study (Participants will be either on medication or off medication to decrease heterogeneity).

6) Implanted cardiac or neurostimulation systems (contraindication to eTNS)

7) Implanted metallic or electronic device in their head (contraindication to eTNS)

8) Presence of body worn devices (e.g., insulin pumps and t-VNS) (contraindication to eTNS)

9) Currently receiving any non-medical treatment (e.g., psychotherapy, counselling, parent-training, cognitive rehabilitation, EEG neurofeedback) (potential confound)10) Participants with dermatitis (could be sensitive to patches)

Additional Exclusion Criteria for the 56 patients that will participate in the fMRI study
11) Not aged between 10-18 years old
12) Have any MRI contra-indications (e.g., metal implants, pacemakers, braces, tattoos/piercings claustrophobia etc.) which would render them unsuitable for the fMRI sub-study

13) Be pregnant or breastfeeding if female

If patients are COVID positive, the participant's involvement in the trial will be delayed. If any patient develops COVID during the trial, arrangements will be made as required for the individual case.

10.3. SELECTION OF PARTICIPANTS

Participants will be recruited from London and surrounding clinics, from Southampton and Portsmouth clinics, parent support groups in London, Portsmouth and Southampton, advertisement and social media. We will also utilise the SLaM Consent for Contact initiative in order to recruit Trust patients and will follow the related Trust policy. We will overrecruit patients who are stimulant medication-naïve or not currently taking stimulant ADHD medication or who are willing to come off their stimulant medication for 1 week before the trial and during the trial. For the optional fMRI part of the project, we aim to include as many participants as possible who are either stimulant medication-naïve or who do not currently take any stimulant medication or are willing to come off for one week before week before the study starts. However, we acknowledge that this may not be feasible, and some may be on stimulant medication.

10.4 CONSENT PROCEDURES

In order to minimise the need for face-to-face meetings, initial consent from parents and assent from the child will be taken digitally by an email or similar. Consent will be obtained by the researchers who will be trained in obtaining them. The researcher will share the information sheet on the screen and go through each section of the information sheet and also each section of the consent form. This would allow for part of the eligibility assessments to be done at the participants convenience in their own home. An ink signature of the consent and assent forms will be obtained at the first visit to the research centre.

10.5. RANDOMISATION PROCEDURE/CODE BREAK

King's Clinical Trials Unit (KCTU) will generate the allocation 1:1 by minimisation by sex , medication, site and age using an online web based KCTU randomisation management system for the duration of the project.
A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.
The CI or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant initials and month and year of birth will be entered on the randomisation system, , email addresses, participant names, addresses, and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial. Randomisation will be done by the researcher once they have confirmed all the baseline measures and ensured eligibility. A blinded notification will be sent to the researcher which will state which device to allocate. All devices have been labelled with individual Device Identification Number (DIN). SAE are very unlikely but will be reported to REC and MHRA and will be reported within 15 days and participants will be unblinded. The trial clinicians will be the first point of contact in case of a SAE (Profs Cortese in Southampton and Prof Santosh in London).

10.6. WITHDRAWAL OF SUBJECTS

There is little evidence for side or (serious) adverse effects of eTNS. Hence withdrawal from the treatment due to adverse effects is not expected. Nevertheless, potential adverse effects have been listed in the participant information sheet which will be provided to participants and their parents for their information. Side and adverse effects will be assessed every week of treatment assessment. Participation in the treatment will be discontinued if

- *the participant decides they no longer wish to continue*
- *recommended by the investigator*

Participants have the right to withdraw from the treatment or from data collection at any time for any reason. Withdrawal from treatment will not constitute withdrawal from data collection unless the participant also wishes to withdraw from data collection. Participants who wish to withdraw from the treatment will be asked to confirm whether they are still willing to provide the study specific data at visits that were completed, and all efforts will be made to continue to obtain follow up data if the participant is willing Reasons for withdrawal from treatment or from data collection will be reported.

10.7. EXPECTED DURATION OF TRIAL

Each participant is expected to be involved with the project for about 7 months from giving consent to the final 6-months outcome measures. The trial is expected to last for 44 months, the first four months is referred to as the setup stage. This is then followed by a 34-month long recruitment period. Following the last visit of the last patient, data will be verified for all participants, corrected if necessary and the database will be locked before the final dataset extraction to be used for the analysis. The data verification and analysis phases are expected to take six months. The trial ends at database lock.

The project started on the 1st of September 2021 and recruitment is expected to start on the 1st of September 2022 due to the delay caused by the need to apply for MHRA approval due to the device no longer having a valid CE mark. Hence, the end date for the project is expected to be end of March 2025 but this may be subject to change.

11. Trial Procedures

11.1. BY VISIT

The following procedure will be followed in this study:

1. The participant will express interest in the study either in response to an advertisement, parent support groups, social media, or through information provided by their clinicians at CAMHs in London, Southampton or Portsmouth, GP practices or through Trust Consent for Contact (C4C) mechanisms.

2. The participant and the parents will then be sent a copy of the information sheet describing the research study and additional information on the methodologies used. They will receive comprehensive information about the study and the type of screening questions that they will be required to answer. They will have to provide consent to the study before the first eligibility appointment that will be online. Consent will be provided by email in the first instance and in paper at the first visit and be collected by the RA at the site.

3. If the participant or the parent contacts one of the researchers (by telephone, digitally, email, or in person) to receive further information, s/he will be given the opportunity to ask any questions about the study, and to take more time to think about it if they so wish. If they express interest in participating in the study, we will take their contact details to arrange a convenient appointment time.

4. Prior to the first testing session, participants will be tested online (Teams) for eligibility or at the research centre. This means the children will be asked to do the verbal part of the IQ test online which will be followed by further

subtests. Their parents will also be asked to fill in some questionnaires on their ADHD behaviours (the ADHD-RS, K-SADS; Conners 3 P-S;). Parents and children will both be interviewed on the K-SADS. This visit will also provide the child and their parent with an opportunity to ask questions about the study and to familiarise themselves with the study protocol and the facilities. The questionnaires will be sent to them beforehand per email and the researcher will go through the questions in the online meeting. In addition, the child can have a mock scan during this visit to see whether they would like to take part in the optional fMRI scan.

5. If the children are eligible to take part in the study, they will then have to come to the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) or to Southampton University, depending on where they live and have been recruited from, to do the first baseline assessment.
This will involve the following:
If this is the first visit to the research centre and the IQ eligibility criteria have not been confirmed, then this will be the first task to ensure the participant is not excluded based on IQ. Once this is confirmed this will then be followed by a brief introduction of the eTNS device to ensure that the child is fully aware of what the eTNS device looks like and how it functions.
Performance of a computer test battery that measures attention, inhibition and timing skills.
The children and their parents will also be asked to fill in some more questionnaires about their behaviours (Parents and children: ARI, BRIEF-2, RCADS 25; children only: MEWS; SDQ, C-SSRS; parents only: SDCS. If they prefer, they will be offered to fill in these questionnaires before they come to the Institute to shorten their visit.
The children and their parents will also be asked to ask their teachers to provide rating of the ADHD-RS and the Conners T-S. Efforts will be made to obtain teacher ratings; however, participants can still be part of the study even if their teachers are unable to complete these measures.
They will be measured on physiological measures such as heart rate, heart rate variability and objective hyperactivity measures in a wrist-held electronic device which they will be sent before the day of testing for 24 hours and bring back to the research centre on the day of baseline assessment.
Pupil diameter (percentage change from baseline measure) and head motion will be measured at rest and during one of the computerised tests.
All participants will be randomly allocated to an experimental (eTNS) and a control group (sham eTNS). The randomisation will be stratified by age, sex and medication status.

6. At the beginning of the trial, the researcher will explain the procedure in detail for how to use the eTNS device Participants and their parents will be given instructions by the RA on how to attach and switch on the eTNS battery device every night before they go to sleep. Both groups will have 4 weeks of treatment with the eTNS device for 8 hours during each night. They will also be asked to fill in a sleep diary every morning over the 4 weeks which should record how many hours they had the eTNS attached.

7. Every week, the parents and children will have to fill in remotely the questionnaires on side effects, the parents will have to fill in the ADHD-RS, and the Conners 3 P-S These weekly assessments will be done remotely. After the first week and the last week, the parents and children will also have to fill in a blinding questionnaire.

8. At the end of the last week, the 4th, the parents will have to fill in several questionnaires about their children's ADHD behaviours and the other parent rated clinical questionnaires, the children will also be asked to fill in some questionnaires about their behaviour, and both will have to fill in the side events questionnaires. (Parents and children: ARI, BRIEF-2, RCADS 25; children only: MEWS, SDQ; C-SSRS; parents only: SDSC. The children and their parents will also be asked to ask their teachers to provide again ratings of the ADHD-RS and the Conners 3 T-S. The children and their parents will have the option to fill in these questionnaires beforehand or remotely (at a maximum delay of 3 days before) to reduce the time spent at the research Institutes.
The children will also do again the computerised tests of attention, inhibition and timing to test whether they have improved in these skills after the training.
They will also be given a blinding questionnaire about which treatment they think they are in and an acceptability survey.
They will be measured again in heart rate, heart rate variability and objective hyperactivity measures in a wrist-held electronic device which they will be sent before the day of testing and which they will have to wear for 24 hours. Pupil diameter and head motion will be measured at rest and during one of the computerised tests.

9. Six months after the treatment, the parents will be asked to fill in (or answer by telephone, digital) the ADHD severity questionnaire, other clinical questionnaires and the child will have to fill in questionnaires about his/her behaviour (Parents and children: ARI, BRIEF-2, RCADS ; children only: MEWS, SDQ; C-SSRS; parents only: SDSC;) and repeat the cognitive test battery one more time. They will be measured again in heart rate, heart rate variability and objective hyperactivity measures in a wrist-held electronic device which they will wear on the day

of testing for 24 hours. Pupil diameter and head motion will be measured at rest and during one of the computerised tests.

10. The participants will receive £50 for the eligibility assessment, and for each of the assessments pre, post and at follow-up (i.e., £150). They will also receive £150 for the 4 weeks of treatment, i.e., in total £350.-
We will give them tokens for each visit throughout the 4-week treatment. They will receive money in exchange for the tokens at the end of the treatment and at the follow-up assessment. For those who are taking part in the optional fMRI scan there will be an additional incentive of £50 for each scan (total £100). We will also reimburse their travel costs.

11.2. LABORATORY TESTS

None.

11.3. BLINDING

The trial manager is planned to be unblinded throughout the trial. The devices will be labelled with random numbers and the trial manager will keep a code as to which device number corresponds to group A or B. Once a participant is randomised, a device is allocated to that participant on the randomisation system.

The devices look identical, and the instructions are identical for both sham and real eTNS. The RA will give the instructions for how to use the device for demonstration purposes.

We will have researchers at each site who will train parents how to use the device. The researchers at each location acting as outcome assessors will be fully blinded to the allocation.

The Junior Trial Statistician will be blinded to the level of treatment until the first draft of the Statistical Analysis Plan (SAP) is approved by the Trial Steering committee. After this point if required by the DMC, they may be partially unblinded (data by unlabelled trial arms, denoted only A or B) or fully unblinded. The Senior Statistician will be fully blinded until after completion of the primary analysis. Following unblinding or partial unblinding of the junior statistician, any required changes to the SAP will be made by the senior statistician only..

11.4 ALLOCATION CONCEALMENT

In the previous studies, some but not all subjects in the active and sham groups reported feeling some sensation, which generally faded with time. In the previous trial, blinding was successful. There was no difference between groups on questions pertaining to belief in having active or sham device (McGough et al., 2019).

To further protect the blind, subjects are counselled during enrolment that stimulation may not be perceptible, and that most people do not feel the stimulation after some time because the scalp adapts to the stimulation.
To assess the success of the blinding, all subjects will be asked to guess which study device they have been using through a blinding questionnaire at their week one visit and at the end of treatment.

A series of precautions will be implemented to ensure the integrity of the blinding process:

1) the sham devices are programmed to have a 60s stimulation of every hour at a low frequency. This is to avoid making it obvious to the participants which device that they have been allocated. 2) the researcher will randomise the participants and the system will allocate a device for that participant
3) the families will be trained using the device by the researchers and be shown on a device. Families are told that the sensory experience may vary from person to person, that some participants do not feel anything, and that prior users have used words like “tingling,” “vibration,” “buzzing,” and “tickling” to describe their experiences. They will also be told that most people do not feel anything after some time because the scalp adapts.
4) participants are instructed to not discuss the experience of using the device with any member of the research team
5) a technical manual will be given to the families on how to use the device and if any queries arise there will be a separate email address and phone number for technical support
6) technical support given to participants will be given at first instant by the trial manager who is unblinded but will follow a pre-set guide regarding support and advice to families. This may at times be covered by the PI who is blinded but will follow the same set of instructions

7) members of the research team will remind participants to not discuss any issues regarding the devices apart from how many hours that they used it each night
8) all assessments will be conducted by blinded staff (post-docs at each site will be blinded).

In the previous US proof of concept trial, participants could not distinguish real from sham treatment (McGough et al., 2019). The blinding was also successful in similar studies with the device in depression. To further enhance the blinding in this study, the first 60s of stimulation will be real in the sham eTNS and then be switched off. The scalp adjusts very quickly to the stimulation and the switch-off is not noticeable.

11.5. MECHANISTIC SUBGROUP

A subgroup of 56 patients who are over 10 years old will also receive an MRI scan of one hour where they will perform 3 short fMRI tasks of 5-10 min and a resting scan of 8 min. They will have to fill in an MRI safety form and be eligible for MRI scanning. This group of participants will receive the first MRI scan before the first treatment week, on the baseline visit. During this visit a parent or guardian of the child will have to fill in the above-mentioned questionnaires. They will receive the second scan after the 4th treatment week on the same day they come in to the IOPPN for filling in the questionnaires and to do the computer tasks.

Fifty-six participants will be scanned twice (at baseline and after 4 weeks of eTNS) on a GE MR750 3T scanner (General Electric Milwaukee, USA) at the King's College London Centre for Neuroimaging Sciences with each scanning session lasting 60 min. They will be scanned in a 6 min resting scan and during 3 well validated and replicated fMRI tasks developed in our lab that target key brain systems that have been shown to be under functioning in ADHD: 1) a task of working memory (5 min) (Cubillo et al., 2013). 2) a 12 min parametric sustained attention task with 3 difficulty levels (Christakou et al., 2013; Kowalczyk et al., 2019) and a 6 min tracking Stop task (Cubillo et al., 2014; Rubia et al., 2005).

We will overrecruit patients in order to obtain 56 sets of useable scans.
They will be reimbursed separately for the MRI scans for which they will receive £50 for each scan (i.e., £100 in total).

11.6. PROTOCOL VIOLATIONS/DEVIATIONS

Patient processes that do not follow the essence of the protocol but are not likely to impact on the findings of the study will be recorded as a file note. Patients that do not follow the processes outlaid in the protocol that may affect the findings of the study are recorded as Protocol Deviation (PD).

All protocol deviations will be reported to the DMC and those deviations that the DMC deemed important will be reported to MHRA.

12. ASSESSMENT OF EFFICACY

12.1. PRIMARY EFFICACY PARAMETERS

The primary endpoint will be the **I**nvestigator-scored parent-rated ADHD symptoms measured on the well validated ADHD-RS at baseline and weekly during the 4 week trial (Dupaul et al., 1998). The ADHD-RS recorded at the 6 months follow up visit will be a secondary endpoint. The clinician/investigator scored parent-rated ADHD-RS is the most commonly used primary outcome measure in treatment trials of ADHD (Cortese et al., 2018). The Post-docs will be trained in obtaining this measure by the clinicians.

12.2. SECONDARY EFFICACY PARAMETERS

Secondary measures are obtained at baseline, after 4 weeks of treatment and at 6 months follow-up except for Conners 3 P-S , side effects and sleep questionnaires which will also be assessed weekly during the 4-week treatment.

1) The teacher-rated ADHD symptoms assessed in the ADHD-RS (10min)
2) Parent and Teacher rated severity of ADHD symptoms using the Conners P/T-S (10 min) (Conners et al., 1998a, b).
3) Self-reported outcome measure Strength and Difficulties Questionnaire (SDQ) (10min)
4) A scale that measures emotional dysregulation, the parent (ARI-P) and child (ARI-S) rated Irritability questionnaire (2min) (Stringaris et al., 2012).

5) A questionnaire that measures the degree of mind-wandering rated by children (MEWS)(5min) (Mowlem et al., 2019)

6) Measures of depression and anxiety assessed in the child and parent rated short forms of the revised Child and Adolescent Depression scale (RCADS-25 and RCADS-25-P) (15min) (Ebesutani et al., 2017; Ebesutani et al., 2012).

7) Measures of the Columba Suicide Severity Rating Scale (10 min) (C-SSRS).

8) Daily Life indicators of Executive functioning measured by the 12 item Behaviour Executive Function Questionnaire- Parent and Self-report measures (BRIEF-2) (15min) (Gioia et al., 2000)

9) Parent-reported sleep quality measured in the parent-reported Sleep Disturbance Scale for Children (SDSC) (10min) (Bruni et al., 1996)

10) Executive functions: performance on a cognitive task battery developed for ADHD (Rubia et al., 2007) including several executive functions using the following measures: (One hour)

a) omission and commissions errors in the CPT sustained attention and the vigilance tasks

b) probability of inhibition in the GNG task

c) Simon RT effect for the Simon interference inhibition task

d) errors in the time estimation task

e) composite measures of mean reaction time, intrasubject standard deviation of reaction time and premature errors across the GNG, CPT and Simon tasks

11) Physiological measures: This measure will only be measured before and after treatment. The specific measures will be:

a. Heart rate, heart rate variability and objective hyperactivity measures will be measured in a wrist-held electronic device for 24 hours (Electrodermal Activity, Heart Rate Variability, Movement Variability).
b. Pupil diameter (and head movement (coordinates of eye position) will be measured at rest for 5 min and during one of the computer tasks.

12) Safety measures: Safety will be assessed through weekly parent and children completed side effects rating scales adapted for eTNS (McGough et al., 2019). (5min). In addition, there will be open questions, asking about general adverse events and their severity during the study period which will be recorded on the adverse events log and reported if needed.

12.3. PROCEDURES FOR ASSESSING EFFICACY PARAMETERS

The primary efficacy measure (ADHD-RS) will be obtained at baseline, weekly over the 4 weeks, and at 6 months follow-up. The questionnaire measures investigator scored parent-rated ADHD core symptoms.

The secondary clinical efficacy measures are questionnaires that will be filled in by teachers (Conners 3 T-S ADHD-RS for teachers) or by parents (BRIEF-2 (P); Conners P-S, ARI-P; RCADS-25-P; SDSC) or by the child (BRIEF-2 (C): C-SSRS ; RCADS-25; ARI-S, MEWS, SDQ) at baseline, post-treatment and at follow up at 6 months. The Conners 3 P-S and SDSC will also be filled in weekly during treatment. The measures are scores in the questionnaires.

The secondary cognitive performance measures will be assessed at baseline, 4 weeks and at 6 months follow-up. They will be performed on a laptop and the outcomes will be dependent variables of performance indicators in the tasks.

Safety measures will be assessed by researchers at each visit by side effects rating scales by parents and children at baseline and weekly, and by adverse events recording.

12.4. Lab measures for monitoring:

Lab measures for monitoring will be weight, height and vital sign measurements at baseline, after treatment and at follow-up.

13. ASSESSMENT OF SAFETY

13.1. SPECIFICATION, TIMING AND RECORDING OF SAFETY PARAMETERS

13.1.1. Safety of the Medical Device (eTNS)

We do not expect any serious or major side effects or adverse events as the device is considered safe in children and only transient and non-serious side events were found in the previous US pilot study which is why the treatment was approved by the FDA for treatment of ADHD and was also CE marked in Europe for ADHD treatment until August 2021 (further detail see section 8.1). The device is labelled class IIA in safety. The most common side effects are transient headaches.

In the two previous US trials in children with ADHD, the safety profile was very favourable, consistent with the previously reported safety profile of the device for use in adults with other mental health or neurological conditions. There were no serious adverse events; adverse events were mild to moderate in clinical significance. No children withdrew due to adverse events. In the open trial, only two adverse events were considered potentially due to eTNS, i.e., headache and eye twitching, and resolved with changing of electrode positioning or spontaneously and did not inhibit participation (McGough et al., 2015). In the RCT, there was an increase in weight and pulse in the active group and notable increases were observed in fatigue, headache, and increased appetite in both real and sham eTNS groups, but these did not differ between groups. Transitory skin discoloration occurred in some darker coloured participants but resolved with exposure to sun light. None of the side effects required clinical intervention or led to early participant withdrawal. There were no scores suggestive of suicidality (McGough et al., 2019). These results supported approval as a minimal risk intervention for ADHD by the U.S. FDA in 2019.

13.1.2. Safety of fMRI

fMRI is considered safe and non-invasive, and no side effects are usually recorded.

A safety form will need to be filled in to ensure patients have no metal in their bodies including braces, metal tattoo and piercings.

However, there is a slight risk that the scanner is sometimes perceived as unpleasant and uncomfortable. The researchers will be sensitive to this possibility and will suspend testing sessions at the request of the participant or at the first signs of distress and discomfort. The participant will be informed that he/she is free to terminate the scanning session whenever he/she wants to. Alerting mechanisms ensure easy communication and radiographers will constantly check that the participant is content to remain in the scanner.
Children and adolescents are sometimes anxious about the scanner − they will be shown the "mock scanner" to familiarise them with the scanner beforehand and they will be able to tell in the first scan whether they are happy to be scanned twice (before and after 4 weeks of treatment). Every effort will be made to ensure that they do not feel anxious or claustrophobic. However, if they feel that the scanner is frightening to them, they will not have to participate. The same applies for adolescents who feel claustrophobic in the scanner.
The scanner is also noisy, and this may be unpleasant for some children. We will therefore expose them to the noise beforehand in the mock scanner. If the children feel that they dislike the noise, they do not have to participate. Also, in order to minimize the discomfort of the noise, we will provide all participants with headphones that are specifically designed for fMRI scanners to reduce the noise level. This is standard procedure for all scanning subjects at the Institute of Psychiatry, Psychology and Neuroscience (IOPPN).

13.2. PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

Adverse Event (AE), Adverse Device Effect (ADE) will be recorded weekly during the treatment in free report and side effects will be recorded weekly in side effects questionnaires. All adverse events/ side effects that need attention at any time will be flagged by the post-docs and reviewed by the relevant local clinician/child psychiatrist (Prof Samuele Cortese in Southampton and Prof Paramala Santosh in London). In addition, all adverse events and side effects will be reviewed during monthly Trial Management Group (TMG) meetings.

Serious Adverse Event (SAE) are very unlikely but will be reported to the main REC and to MHRA should they occur within 7 days and participants will be unblinded.

All SAEs, Suspected Serious Device Effect (SADE) and Unanticipated Serious Adverse Device Effect (USADE) (excepting those specified in this protocol as not requiring reporting) will be reported immediately to the Chief Investigator and to the Sponsor, REC and MHRA.

	Who	When	How	To Whom
SAE **SADE** **USADE**	Chief Investigator	Within 7 days of CI becoming aware of the event	SAE Report form for Non-CTIMPs, available from NRES website. Reporting to MHRA will be using the MEDDEV 2.7/3 SAE Report table	Main REC with a copy to the sponsor and DMEC Chair. The sponsor will report to MHRA.
Urgent Safety Measures	Chief Investigator	Immediately Within 3 days	By phone Notice in writing setting out reasons for the urgent safety measures and the plan for future action.	Main REC Main REC with a copy sent to the sponsor. The REC will acknowledge this within 30 days of receipt. The sponsor will report to MHRA.
Progress Reports	Chief Investigator	Annually (starting 12 months after the date of favourable opinion)	Annual Progress Report Form (non-CTIMPs) available from the NRES website	Main REC with a copy to the sponsor
Declaration of the conclusion or early termination of the study	Chief Investigator	Within 90 days (conclusion) Within 15 days (early termination) *The end of study should be defined in the protocol*	End of Study Declaration form available from the NRES website	Main REC with a copy to the sponsor, MHRA
Summary of final Report	Chief Investigator	Within one year of conclusion of the Research	No Standard Format However, the following Information should be included:- Where the study has met its objectives, the main findings and arrangements for publication or dissemination including feedback to subjects	Main REC with a copy to be sent to the sponsor, MHRA

13.2.1. Adverse events that do not require reporting

In case of any serious adverse events (SAE) standard HRA reporting procedures will be followed. Related and/or unexpected SAE will be reported to the relevant Research Ethics Committee within 15 days of the Chief Investigator becoming aware of the event. All other safety reporting, including progress reports, declaration of conclusion, and summary of final report, will be performed according to the HRA guidelines.

13.3. STOPPING RULES

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the Data Monitoring Committee (DMC) to the Trial Steering Committee (TSC) (), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor. If the study is prematurely discontinued, active participants will be informed and no further participant data will be collected.

13.4 INTERNAL PILOT

At 19 months after start of the project (15 month after recruitment started) after the first site is opened to recruitment, an internal pilot will be carried out to demonstrate feasibility of the study. The following progression criteria will be presented to the DMC.

Recruitment	Red < 60%	Amber (60-80%)	Green > 80%
Recruitment of (n=75)	< 45	45-60	> 60

There is no planned formal interim analysis to assess efficacy within the study. However, trial progress will be presented to the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) following the TSC terms of reference and DMC Charter.

14. STATISTICS

A full statistical analysis plan will be drafted in accordance with the KCTU Standard Operating Procedures authored and reviewed by the Junior and the Senior Statistician, respectively, and approved by the Trial Steering Committee.

The SAP should be detailed enough so that it presents a clear and structured plan for the primary outcome, required data manipulation, and analysis. All changes to the SAP after approval by the TSC should be authorised by a statistician who is fully blind, this would be the Senior Statistician.

14.1. SAMPLE SIZE

Proposed sample size: N = 150.

For the primary outcome measure:

Based on the previous trial, we anticipate a between group reduction in ADHD symptoms at 4 weeks between real eTNS versus sham with an effect size = 0.5 (McGough et al., 2019). Using a baseline to post-treatment correlation = 0.5, with 90% power, and a 5% type I error, we estimate that we will need to recruit 128 participants (64:64). In order to account for a loss to follow up rate of 15% (which is a conservative estimate given our attrition rate of 9% for our fMRI Neurofeedback trial and of 0% for our tDCS trial), we have inflated the number randomised to 150 (75:75).

Using fMRI for the mechanistic outcome measure: we aim to detect a large between group effect of 0.7 (lower than the previously detected effect sizes of 2 and 2.4 based on a within-subject design on stimulant medication effects in the same Stop and sustained attention tasks, respectively; (Cubillo et al., 2014; Kowalczyk et al., 2019) in a pre-post design, assuming a correlation of 0.7 (pre-post). In order to detect this difference with 90% power, at the 5% significance level we will need 44 participants. Assuming a loss to follow up of fMRI of 20% we will inflate the numbers included to 56 (28:28).14.2. RANDOMISATION

King's Clinical Trials Unit (KCTU) will generate the allocation by minimisation by sex(male/female), medication status (on medication; off medication/naïve), site (KCL, Southampton) and age (8-13 years, 6 months; 13, 6 months to 19 years) using an online web-based system. Members of the research team will randomise a participant once all baseline measures are collected and eligibility confirmed. There will be a blinded notification and confirmation that the participant has been randomised and allocation of the device sent out to all research team members.

14.3. ANALYSIS

Primary outcome analysis: The primary analysis will be analysed using a mixed-effects linear model, fitting 4-week ADHD symptoms scores, each patient will be fitted as a random intercept, and adjusted for fixed effects of baseline ADHD score, site, age, gender, and medication. We will estimate 95% confidence intervals and p-values and effect sizes for the between group post-baseline difference will be assessed with two-sided test with alpha=0.05.

Secondary analyses: Secondary outcome of continuous data will be analysed consistently with the primary outcome. Dichotomous secondary outcomes will be analysed using a logistic regression, adjusted for the same covariates as within the primary outcome.

Longer-term Follow up: All outcomes will be repeated at 6 months follow up. These will be analysed with linear and logistic regression analyses. The outcome will be the 6-month time-point, and these will be adjusted by: baseline score, site, age, sex, medication, and adherence,

Populations under investigation and missing data:

A modified intention to treat (ITT) population will include all patients randomised with at least one post baseline weekly assessment of the primary outcome. The primary analysis will use the ITT population. Missing baseline data will be negligible.If we do observe missing data, we are following an approach set out to handle missing data by Jakobsen et al (2017). We will use longitudinal models for the primary analysis using maximum likelihood estimation, and baseline predictors of missingness will be included as covariates. If post-baseline variables are predictive of missingness, inverse probability weighting will be used. Thus, the primary analysis will be unbiased under a missing at random assumption.

As per Jacobsen et al (2017) “There is no way to distinguish between missing data that is missing at random versus missing not at random as by definition the missing data is are unknown and it therefore cannot be assessed if the observed data can predict the unknown data”, and consequently “The validity of methods used to handle MNAR data require certain assumptions that cannot be tested based on observed data”. As such, and as recommended by Jacobsen et al (2017), we are making a missing at random assumption for the primary analysis, but in the presence of missing data, we will carry out sensitivity analyses looking at the best- and worst-case scenarios for the theoretical range of unobserved missing values under a missing not at random assumption. This approach is also consistent with ICH E9. This will be outlined in the Statistical Analysis Plan which will be written by fully blinded analysts and will be approved by the Data Monitoring Committee and the Trial Steering Committee.

Sensitivity analysis: A sensitivity analysis of the primary outcome will be carried out to estimate the treatment effect in those participants who complied to the intervention, using a per-protocol-analysis.

Mechanistic Analysis

Structured mediation analyses will be conducted to explore potentially mediating effects of brain function and cognitive measures on the clinical outcome.
Logistic regression models will be used to test predictors of response based on clinical, imaging, cognitive and physiological (heart rate and pupil diameter) measures using a reduction of 20% or more in clinical ADHD-RS symptoms as a typical indicator of treatment response as per NICE guidelines.

For fMRI analyses, non-parametric FSL RANDOMISE analysis package will be used (http://www.fmrib.ox.ac.uk/fsl/). Functional connectivity analyses will use thalamus, basal ganglia and lateral and medial frontal regions as seed regions to test our hypothesis that task-relevant fronto-striato-thalamic networks will be up-regulated with eTNS. We will also use LC as seed region for our hypothesis that LC-frontal connections will be increased with eTNS. For the resting state fMRI analysis, we will use regions of interest of the default mode network (reflecting mind-wandering), and of dorsal and ventral attention and cognitive control networks to test our hypothesis of increased functional connectivity in these networks with eTNS and of the increased anti-correlation between these networks and the default mode network.

15. TRIAL STEERING COMMITTEE

The Trial steering Committee (TSC) will meet between 6 monthly to annually, by a variety of online and face-to-face meetings. TSC will report to the EME Programme. Its purpose is to provide overall supervision of the trial, approving the protocol and amendments, monitoring adherence to the protocol, and providing independent advice on all aspects of the trial. Observers from the EME Programme will be invited to all TSC meetings.

Composition:

1) It will be chaired by an independent senior clinician chair and include
2) 2 further independent clinical academics
3) An independent trial statistician
4) PPI: a mother of a child with ADHD, an adult with ADHD and an adolescent with ADHD.
5) The lead investigators of each site will attend as part of the non-independent members (Profs Rubia and Cortese).

16. DATA MONITORING COMMITTEE

The DMC will meet between 6 months to annually depending on the stage of the study before the TSC meeting. Both face-to-face and online meetings are planned. It will monitor the safety, ethical conduct, protocol deviations and quality of the data. It will have access to all trial data and will receive regular reports on adverse events. The role of the DMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants’ attention or any reasons for the trial not to continue. The DMC will be independent of both the investigators and the funder/sponsor and will be the only body that has access to unblinded data if needed. It will make recommendations to the TSC. The independent DMC can advise discontinuation of the trial, e.g., because of safety concerns about the trial. DMC will have access to the database detailing all Adverse Events (AEs) and Serious Adverse Events (SAEs). Membership of the DMC will be independent of the applicants

and of the TSC. The DMC will be notified of any serious adverse events (which are unlikely) as they occur and will consider whether any interim analyses are warranted, review data and advise the TSC on any ethical or safety reasons why the trial should be prematurely ended. Administrative support to the DMC will be provided by the study team.

Composition:

1) It will be chaired by an independent international expert experienced in conducting clinical trials with child mental health populations
2) It will also comprise an independent senior trial statistician
3) another independent senior clinician

17. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

All measures will be recorded on hard copies either by the participants and their parents or the measures will be recorded by the researcher onto hard copies during a digital session with participants. These hard copies will be the source data. Data obtained from measure such as vital signs, height, weight, pupil diameter, head movement, and heart rate variability and electrodermal activity will be recorded by the researchers on a hard-copies and electronic records and this will be the source data. The hard copies will contain the participants identification number, date that the measures were obtained and the initials of the researcher obtaining the measure. All data from the hard copies will be entered onto the database apart from the fMRI scan data that will be stored separately and will be the source data. The Investigators will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (e.g., patients' clinical or other data).

18. ETHICS & REGULATORY APPROVALS

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the UK policy framework for health and social care research and the Mental Capacity Act 2005.

This trial and related trial documents have been reviewed and approved by West Midlands- Solihull Research Ethics Committee (REC) (ref: 21/WN/0169) and Health Research Authority (HRA).

Subsequent amendments will need to be approved by REC and HRA. In addition, approval from Medicines and Healthcare products Regulatory Agency (MHRA) is required. The Chief Investigator will submit a final report at conclusion of the trial to the funder, the REC, MHRA and the Sponsor.

19. QUALITY ASSURANCE

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed by the Trial Management Group (TMG). All staff members will be trained in Good Clinical Practice (GCP) and General Data Protection Regulations (GDPR). SPIRIT statements have been followed in the protocol. Statistical processes will follow King's Clinical Trials Unit Standard Operation Procedures. There will be a trial management group (TMG), a Trial steering committee (TSC) and a Data Monitoring Committee (DMC). The Trial Management Group (TMG) will meet monthly, its membership will include the CI and Co-Is, the trial manager, research staff and members of PPI. It will be chaired by the CI and the trial manager will manage the day–to-day running of the study and ensure good communication between the 2 trial sites, receiving monthly reports from each site on recruitment, adherence, side and adverse events, reviewing progress against milestones and finding solutions to problems as they arise. If needed report to the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMC) (see above).

20. DATA HANDLING

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised. All anonymised data will be stored on a password protected computer.

- All trial data will be stored in line with the Data Protection Act.

- and archived in line with Sponsor requirements
- Audio-recordings (for the K-SADS) are necessary for quality control and for potential queries regarding diagnosis which can be checked with the CO-I clinicians. Recordings will be taken on a password protected encrypted smartphone as per South London and Maudsley (SLAM) Secure Voice Recordings guidelines and which will be provided by KCL for the purpose of this study. Only the study team will have access to the smartphone. Participants will provide an opt-in consent to have their recordings taken. Where participants will decide not to have their recordings taken this will not disqualify them from the study. The recordings will be kept on a password protected KCL PC in an anonymised format (as described in the above). Audio-recordings will be destroyed upon completion of the study. Nonetheless, participants will have the option to request to have their information (i.e., audio-recordings and any other material generated by the study) destroyed at any time.

21. DATA MANAGEMENT

All investigators and researchers will comply with the requirements of the Data Protection Act 2018 and GDPR with regards to the collection, storage and processing. The data will be demographic data, clinical assessment and questionnaire data, behavioural outcome data, cognitive performance data, physiological data, heart rate data, eye-tracking data, and fMRI data in electronic format and password protected. The data from E4 Empatica wristband and Tobii Pro eye tracker will be pseudoanonymised (dummy information such as dummy name and email addresses) and be entered onto these platforms.

The data to be analysed will be inputted into the below described Macro system in a linked-anonymised format.

Data management will follow KCL guidelines.

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant initials and month and year of birth will be entered on the EDC. , email addresses, participant names, addresses and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by recruiting site staff typically within 30 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The trial manager will undertake appropriate reviews of the entered data, in consultation with the project analyst for the purpose of data cleaning. The trial manager will only have data monitoring access and will raise Source Data verification (SDV) for any discrepancies found which the researchers with data entry access can address appropriately. Should any amendments to the database be required this will be agreed within the TMG and the changes agreed by the CI, statisticians and trial manager and any corrections be made by the research staff.

fMRI data will be acquired according to standard protocols, and subject to on-going calibration and quality control procedures within the CNS at the IOPPN. fMRI imaging data will be linked by ID to clinical, demographic and neuropsychological data. For all the processing currently envisaged, data will be processed and stored in NifTI format (http://nifti.nimh.nih.gov/), allowing it to be easily read by most current neuroimaging research packages, allowing data-sharing and ensuring long-term data validity.

For the randomisation system, no data can be amended in the system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

At the end of the trial, the statistician will confirm that all data queries are resolved and verify that all the data are complete and correct. At this point, all data entry access will be removed, a final data extraction will be requested, and the database locked. The KCTU will provide a copy of the final blinded dataset to the statistician and trial manager and after the primary analysis the unblinded information will be requested. The statisticians will provide a statistical analysis report to the CI, trial manager and the research team.

22. PUBLICATION POLICY

The results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals, ADHD Guideline groups, and to the public via media communications, social networks, presentations at science festivals, charities, parent and patient support groups, and clinics. Findings will also be disseminated via the KCL website.

23. INSURANCE / INDEMNITY

A professional indemnity policy is in place from the sponsor (KCL) for all studies conducted at KCL.

24. FINANCIAL ASPECTS

This project is funded by the Efficacy and Mechanism Evaluation (EME) programme, an MRC and NIHR partnership (project ref: NIHR130077)

Professor Katya Rubia has received a grant from Takeda Pharmaceuticals for another project and speaker's bureau from Lundbeck and Supernus which were paid to King's College London and used for research.

Professor Samuele Cortese has received honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP) and from healthcare Convention for educational activity on ADHD.

Professor Mitul Mehta has received research funding from Takeda Pharmaceuticals, Johnson and Johnson, Lundbeck and Heptares. Also, he acted as a consultant for Neurocrine and Lundbeck.

Professor Santosh Paramala is the CEO of HealthTracker Ltd which provides web-based health monitoring solutions. He has also received research funding for conducting clinical trials in Rett Syndrome from Anavex Scientific Corp, GQ Pharma and Newron Ltd.

Dr Ben Carter and Andrea Bilbow have no financial interest to declare.

25. CONFIDENTIALITY AGREEMENT

When consent forms are signed, a copy will be provided to the patient, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant initials and date of birth will be entered into the study database, but no more identifying information will be collected outside the recruiting study site. Within site, an Investigator Site File will be maintained by the site PI. Participants will be fully identifiable within these files.

26. Data sharing statement

A data sharing dataset will be created from the raw data by the study analyst, which will not include participant initials, date of birth or any other identifiable data and study PIN will be altered so that individuals are not recognisable from the dataset.

The study will comply with the General Data Protection Regulations (GDPR).

27. SIGNATURES

Chief Investigator	Date
Print name	
Co-Investigator at University of Southampton	Date
Print name	
Statistician (if applicable)	Date
Print name	

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