Trial Name:

Acceptability and feasibility of transcranial direct current stimulation therapy as a community-based treatment for major depression

NCT number:

NCT03632434

Document date:

25/05/2021

1 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim is to demonstrate the feasibility and acceptability of a course of tDCS sessions for community-based major depression.

1.1 Primary objective

The primary objective is to assess the feasibility of the present trial in terms of study participant retention.

1.2 Secondary objective

To secondary objective is to assess the acceptability of the tDCS sessions.

1.3 Outcome measures/endpoints

Participant retention following enrolment.

1.4 Primary endpoint/outcome

The hypothesis is that there will be participant retention of 70% or greater.

1.5 Secondary endpoints/outcomes

The hypothesis is that participants will positively endorse the tDCS sessions at the end of the trial as measured by an acceptability questionnaire scale.

1.6 Exploratory endpoints/outcomes

Exploratory measures:

i. Trained rater measure of depressive symptoms: Hamilton Rating Scale for Depression (HRSD): The hypothesis is that course of tDCS treatment will improve clinical response as measured by a HRSD score reduction of $\geq$ 50% following the course of tDCS treatment.
ii. Self-report measure of depressive symptoms: Patient Health Questionnaire (PHQ-9)
iii. Trained rater measure of anxiety symptoms: Hamilton Anxiety Scale (HAMA)
iv. Trained rater measure of manic symptoms: Young Mania Rating Scale (YMRS)
v. Self-report measure of disability and impairment: Sheehan Disability Scale (SDS)
vi. tDCS Adverse Events Questionnaire (AEQ)
vii. Participant acceptability questionnaire scales
viii. Optional EEG recordings during an eyes-closed resting state for 10 minutes followed by a decision making task (eg. Cheng and Lee, 2015) and an emotional valence categorisation task (eg. Maeoka et al., 2012).

Exploratory outcomes:

1) HRSD reduction $\geq$ 50% following the course of tDCS
2) HRSD score $\leq$ 7 following the course of tDCS
3) Improvement in self-reported depressive symptoms as measured by PHQ-9
4) Improvement in anxiety symptoms as measured by HAMA
5) No significant increase in manic symptoms as measured by YMRS
6) Improvement in disability experience as measured by SDS
7) Recording of adverse events as measured by the tDCS AEQ
8) Measure of neural connectivity using resting state EEG, which has been proposed as potential surrogate outcome measure for clinical applications (Alhaj et al., 2011; Miniussi et al., 2012; Woods et al., 2016). Quantitative EEG analysis of the decision making task (eg. Cheng and Lee, 2015) and emotional valence categorisation task (eg. Maeoka et al., 2012).

1.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint of evaluation of this outcome measure
Primary Objective To assess the feasibility of the present trial in terms of participant retention	Participant retention $\geq$ 70%	End of tDCS sessions (visit 21)
Secondary Objective To assess the acceptability of the intervention	Positive endorsement of tDCS sessions as measured by an acceptability questionnaire	End of tDCS sessions (visit 21)

2 TRIAL DESIGN

The trial is a pilot, open-label, single arm trail to determine the feasibility and acceptability of tDCS for major depression within a community-based setting.

3 PARTICIPANT ELIGIBILITY CRITERIA

3.1 Inclusion criteria

- participants capable of giving informed consent
- male and female
- minimum of 18 years of age
- diagnosis of major depressive disorder based on DSM-5 criteria, with a current depressive episode of at least a moderate severity
- diagnosis will be determined by the Mini-International Neuropsychiatric Interview
- severity will be assessed using the HRSD with a minimum score of 16 indicating at least a moderate severity of symptoms
- taking antidepressant medication or being involved in psychological therapy.

3.2 Exclusion criteria

- treatment resistant depression as defined by a poor clinical response to 2 or more antidepressant trials
- any concurrent psychiatric disorder, including bipolar disorder or any psychotic disorder
- having a significant risk of suicide
- exclusion criteria for tDCS, including having a scalp or skin condition (e.g. psoriasis or eczema); if contact with the scalp is not possible; having metallic implants, including intracranial electrodes, surgical clips, shrapnel or a pacemaker
- history of epilepsy
- history of a seizure which resulted in a loss of consciousness
- neurological disorder or history of migraines

4 TRIAL PROCEDURES

The Schedule of Events is presented in table format in Appendix 2.

4.1 Recruitment

Recruitment will be from primary care, consulting psychiatrists, print and social media advertisements.

4.1.1 Participant identification

Potential participants will be referred by their GPs and psychiatrists as well as recruited by publicity, leaflets and websites.

Only a member of the patient's existing clinical care team will have access to patient records without explicit consent in order to identify potential participants, to check whether they meet the inclusion criteria and to make the initial approach to patients.

Participants will be identified by their responsible physician or will be identified by self-referral. All participants will be required to be under the care of a GP for study participation.

4.1.2 Screening

The screen assessment requires a DSM-5 diagnosis of major depressive disorder by a MINI interview assessment and a minimum score of 16 on the HRSD. The maximum duration between screening and recruitment is 20 days.

4.1.3 Payment

Participants will be reimbursed for reasonable travel expenses up to £15 as a voucher per visit. Participants will be reimbursed a £5 voucher for each 30 minute tDCS session for their time, which will be a total of £105 in vouchers for 21 sessions, and will be reimbursed a £10 voucher for each of the optional EEG sessions (visits 1, 10, 21), which will be a total of £30 in vouchers for 3 EEG sessions.

4.2 Consent

The Chief Investigator (PI) retains overall responsibility for the conduct of research which includes the taking of informed consent of participants at their site. The PI will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site.

The right of a participant to refuse participation without giving reasons will be respected.

The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and will be provided with a contact point where he/she may obtain further information about the trial. Data and samples collected up to the point of withdrawal will only be used after withdrawal if the participant has consented for this. Any intention to utilise such data is outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant, the PI will ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

The potential participant will discuss with an individual knowledgeable about the research about the nature and objectives of the trial and possible risks associated with their participation. The potential participant will have the opportunity to ask questions.

The written material (information leaflet and consent document) is approved by the REC and id in compliance with GCP, local regulatory requirements and legal requirements

All participants will be capable of giving consent for themselves:

- understand the purpose and nature of the research
- understand what the research involves, its benefits (or lack of benefits), risks and burdens
- understand the alternatives to taking part
- be able to retain the information long enough to make an effective decision.
- be able to make a free choice
- be capable of making this particular decision at the time it needs to be made

4.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable: N/A

4.3 The randomisation scheme: N/A

4.3.1 Method of implementing the randomisation/allocation sequence: N/A

4.4 Blinding: N/A

4.5 Emergency Unblinding: N/A

4.6 Baseline data

The baseline data consist of: HRSD, PHQ-9, HAMA, YMRS, SDS, tDCS AEQ, Acceptability questionnaire, EEG (optional) (Appendix 2).

4.7 Trial assessments

Trial assessments are described in Appendix 2.

4.8 Long term follow-up assessments

Long term follow-up assessments will be acquired at 3 months and at 6 months following the final treatment visit (Appendix 2).

Participants who do not respond to repeated attempts at contact will be identified as 'lost to follow-up'.

4.9 Qualitative assessments

At the final tDCS session, participants will complete the acceptability questionnaire and provide feedback on their experience of the study.

4.10 Withdrawal criteria

Participants will be withdrawn from the trial if they do not comply with the intervention, namely if they are unable to have a minimum of 50% of the tDCS session (10 out of 21 sessions), or if they develop serious adverse effects from any part of the study. Recording of the reasons for withdrawal will be made. Their GP will be informed about their withdrawal, and there will have a telephone follow up at 1 month following their withdrawal.

4.11 Storage and analysis of clinical samples: N/A

4.12 End of trial: N/A

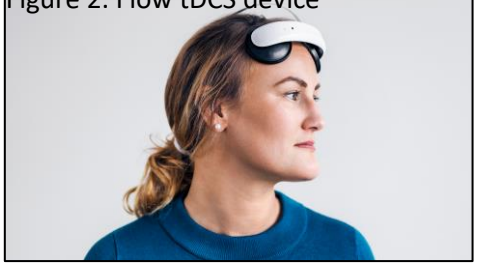
Figure 1. StarStim tDCS device

5 TRIAL TREATMENTS

5.1 Name and description of intervention(s) under investigation

We will use the Neuroelectrics StarStim tDCS device (Figure 1) and the Flow Neuroscience Flow tDCS device (Figure 2). The tDCS device consists of two electrodes through which the stimulation is applied (anode electrode) and through which the stimulation is returned (cathode electrode), which creates a circuit.

Figure 2. Flow tDCS device



In the StarStim tDCS device, the electrodes are fitted within a flexible neoprene cap, and there are different cap sizes (small, medium, large) to account for different head sizes. There are additional spaces within the cap through which the EEG acquisition can be made.

The Flow tDCS device consists of an adjustable headset with the tDCS electrodes built in.

Figure 3. Soterix tDCS device

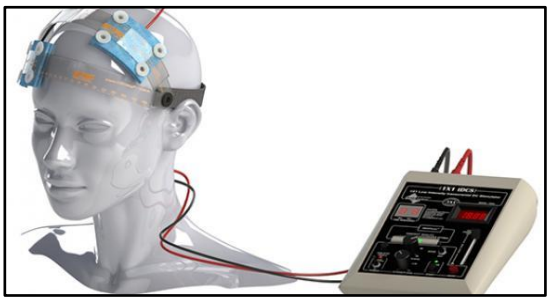
5.2 Regulatory status of the drug (if applicable): N/A

5.3 Product Characteristics:

The Neuroelectrics StarStim tDCS device does not have CE mark approval for the treatment of major depression. The Soterix tDCS device is a similar device which has CE mark approval for the treatment of major depression (Figure 3).

However, the Soterix tDCS device does not incorporate the EEG electrodes within the device, in contrast to the Neuroelectrics Starstim tDCS device which provides a combined tDCS and EEG system within a simply designed, soft neoprene cap.

The Neuroelectrics Starstim tDCS device is portable and provides an ease of use in a simple design which allows EEG acquisition, which will facilitate its use in the community. The Flow tDCS device is portable and commercially available. Both devices can be programmed to provide the specific stimulation parameters for the study. The primary outcome of the study is to assess the feasibility and acceptability of tDCS sessions within the community.



Clinical efficacy of tDCS treatment for major depression

depression is not the primary outcome for the present study, which is not powered to investigate efficacy. The findings from the present study will be applied to design a multi-site randomised sham-controlled clinical trial, which will be powered to investigate efficacy.

5.4 Drug storage and supply (if applicable): N/A

5.5 Preparation and labelling of Investigational Medicinal Product (if applicable): N/A

5.6 Dosage schedules:

The electrodes will be placed in a bifrontal montage, in which the anode is placed over the left dorsolateral prefrontal cortex (DLPFC) and the cathode is placed over the right DLPFC. This is

equivalent to the EEG positions at F3 and F4, respectively. The stimulation will be 2 mA, and the electrode area is 35 cm^2.

Participants will receive a 6-week course of active tDCS treatment, consisting of 5 sessions per week for the first 3 weeks followed by 2 sessions per week for 3 weeks, for a total of 21 tDCS sessions. The duration of each session is 30 minutes.

The tDCS parameters are based on meta-analyses (Meron et al., 2015; Brunoni et al., 2016; Mutz et al., 2018) which demonstrate that treatment effects are most evident at 2 mA current of 30 minute stimulus duration for 21 sessions for participants with recurrent major depression.

During the first session, participants will be taught by the study team how to fit the cap and deliver the tDCS treatment to themselves. During each session, the participant will be seated comfortably, and the research assistant will provide a discreet presence without interacting with the participant. The research assistant will supervise sessions either in person or via video link. Research assistants and participants will wear appropriate PPE during any sessions conducted at the study site or where the research assistant is present in person.

5.7 Dosage modifications: N/A

5.8 Known drug reactions and interaction with other therapies: N/A

5.9 Concomitant medication

If a participant wishes to begin another treatment while taking part in the study, we will continue with the tDCS treatment and we will continue with their follow up care.

5.10 Trial restrictions

There are no known contraindications whilst on the active phase of the trial including dietary requirements or restrictions.

5.11 Assessment of compliance with treatment

The tDCS device records the duration of each session, and there is an automatic shut-off to prevent unsafe use. The equipment will be programmed to provide only the type of stimulation, intensity and session length that are specified in the protocol. The placement is determined by the location of the electrodes which are fitted to specific locations in the cap. The research assistant will be present at each session, in person or via video link, in order to aid in the initial positioning and to monitor for any adverse events.

5.12 Name and description of each Non-Investigational Medicinal Product (NIMP): N/A

6 RECORDING AND REPORTING OF ADVERSE EVENTS

6.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to the intervention.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an intervention which is related to any dose administered to that participant.

	The phrase "response to an intervention" means that a causal relationship between an intervention and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the intervention qualify as adverse reactions.
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 Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to the trial intervention, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the intervention.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Detailed guidance can be found here:
http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

6.2 Operational definitions for (S)AEs

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In all cases AEs and / or laboratory abnormalities that are critical to the safety evaluation of the participant must be reported to the Sponsor; these may be volunteered by the participant, discovered by the investigator questioning or detected through laboratory test or other investigation. Where certain AEs are not required to be reported to the Sponsor, these will still be recorded in the participant's medical records.

6.3 Recording and reporting of SAEs, SARs AND SUSARs

All serious adverse events will be recorded in the CRF as well as in the trial database, from which a line listing of SAEs can be extracted for review. The line-listing of SAEs will be reported to the Sponsor once per year.

All SAEs must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete the Sponsor's SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible.

Where the event is unexpected and thought to be related to the intervention, this must be reported by the Investigator to the Health Research Authority within 15 days.

For each SAEs the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator
- whether the event would be considered anticipated

6.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for tDCS sessions and at follow up.

1. Using medical judgement in assigning seriousness and causality and providing an opinion on whether the event/reaction was anticipated.
2. Ensuring that all SAEs are recorded and reported to the Sponsor.
3. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
3. Immediate review of all SUSARs.
4. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol.

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit.
3. Notifying Investigators of SUSARs that occur within the trial.

6.5 Notification of deaths

All deaths, including deaths deemed unrelated to the study, will be reported to the Sponsor within 24 hours of notification.

6.6 Pregnancy reporting

All pregnancies within the trial (either the trial participant or the participant's partner, with participants consent) will be reported to the Principal Investigator and the Sponsor.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

6.7 Overdose: N/A

6.8 Reporting urgent safety measures

If any urgent safety measures are taken the Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

6.9 The type and duration of the follow-up of participants after adverse reactions.

For 3 months after the last tDCS to the participants, adverse events and reactions be recorded and reported.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after the reaction has occurred until resolved.

6.10 Development safety update reports

The Chief Investigator will provide Development Safety Update Reports (DSURs) once a year throughout the clinical trial, or as necessary, where relevant to the REC and the Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

7 STATISTICAL ANALYSIS PLAN

7.1 Sample size calculation

We will enrol 30 participants with major depression based on a 20% attrition rate to achieve a sample size of 24 participants who will complete the course of treatment, given the exploratory nature of the pilot study.

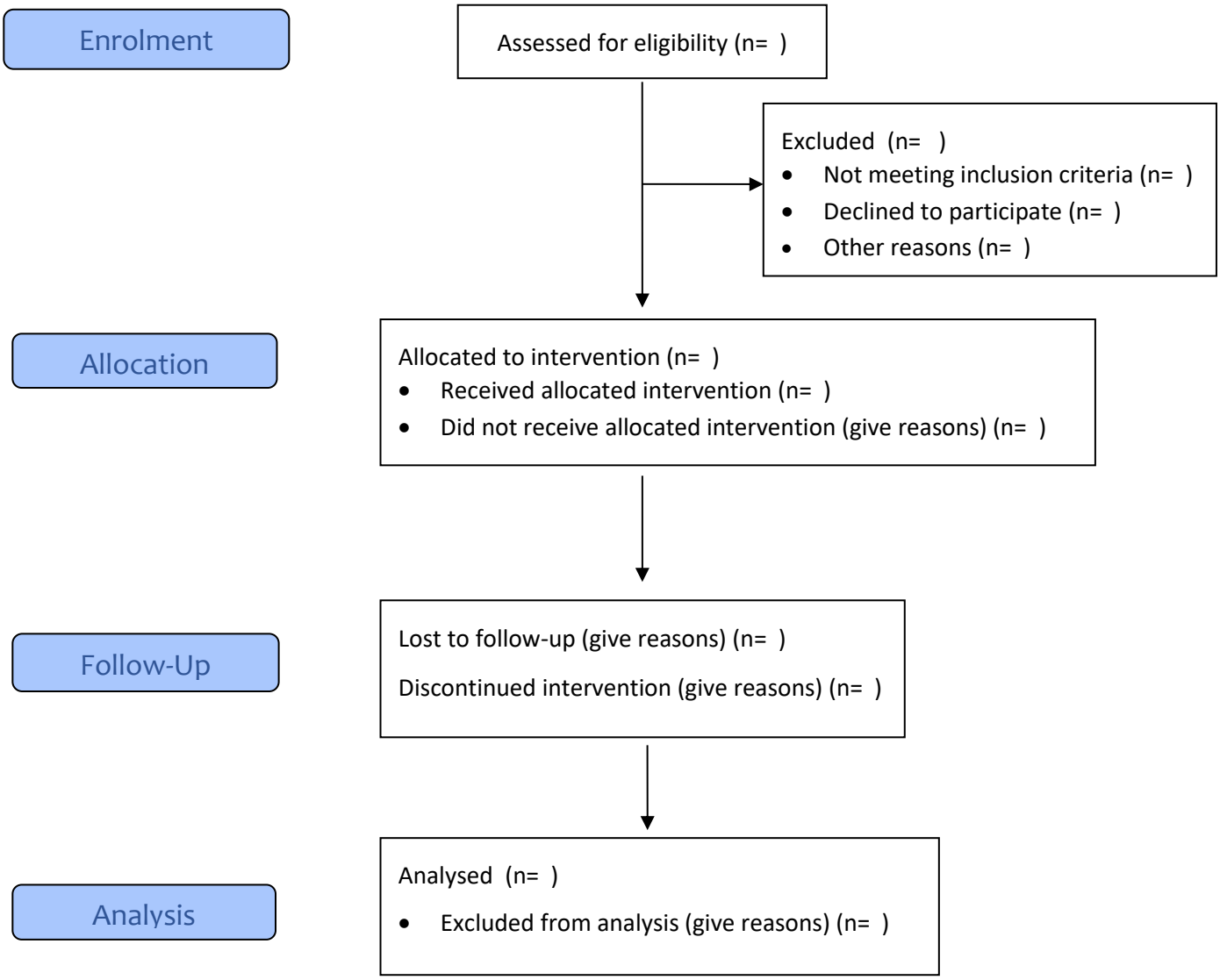
7.2 Planned recruitment rate

The planned recruitment rate is 1-2 participant/s per month.

7.3 Statistical analysis plan

7.3.1 ummary of baseline data and flow of patients

Consort Flow Diagram:



7.3.2 Primary outcome analysis

The primary outcome analysis is participant retention which will be measured by the number of enrolled participants who do not drop out before the 6 week course of tDCS, divided by the total number of enrolled participants, expressed as a percentage.

7.3.3 Secondary outcome analysis

The secondary outcome analyses will be the percentage of participants rating the intervention as acceptable at the end of the 6 week course of tDCS. The acceptability scale consists of the question 'How acceptable did you find the tDCS sessions?' with responses ranging from 'Very unacceptable' to 'Very acceptable' on a 7-point anchored Likert scale with the acceptable ratings being from rating 5-7.

7.4 Subgroup analyses: N/A

7.5 Adjusted analysis: N/A

7.6 Interim analysis and criteria for the premature termination of the trial: N/A

7.7 Participant population

All participants will be included in the analysis in an intention to treat analysis and participants who have completed the study will be included in a completer analysis.

7.8 Procedure(s) to account for missing or spurious data

Any missing data will be imputed in a last observation carried forward model.