Trial Name:

Community-based transcranial direct current stimulation treatment for bipolar depression

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Contents

TRIAL SUMMARY

Trial Title:	Community-based transcranial direct current stimulation treatment for bipolar depression	
Short Title:	Transcranial direct current stimulation therapy for bipolar depression (b-DEP)	
Trial Design:	Pilot, open-label, single arm design	
Trial Participants:	Participants will have a diagnosis of Bipolar disorder, in a current depressive episode of moderate severity, receiving pharmacological or psychological treatment, ages minimum 18 years, community-dwelling.	
Total number of participants planned:	50	
Treatment duration:	6 weeks	
Additional follow up duration:	3 months	
Total trial duration per participant:	5 months	
Estimated total trial duration:	1 year	
Planned trial sites:	Multi-site	
	<u>Objectives</u>	<u>Outcome Measures</u>
Primary Objective:	To assess the efficacy of tDCS treatment	clinical response as measured by MADRS score improvement of >= 50% following the course of tDCS treatment
Secondary Objective:	To assess acceptability and safety of the intervention.	Participant retention at the end of the treatment who have completed a minimum of 15 tDCS sessions. Participant acceptability questionnaire scales tDCS Adverse Events Questionnaire at each session
Formulation, Dose, Route of Administration	Transcranial direct current stimulation (tDCS) device with a bifrontal montage at left dorsolateral prefrontal cortex (DLPFC) and cathode at right DLPFC (EEG positions F3 and F4, respectively). Stimulation is 2 mA, and electrode area is is 35 cm2. The intervention consists of a 6-week course of active tDCS, 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.	

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CE	Conformité Européene (European Conformity)
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EEG	electroencephalogram
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
HAMA	Hamilton Anxiety Scale
HRSD	Hamilton Rating Scale for Depression
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MADRS	Montgomery–Åsberg Depression Rating Scale
MHRA	Medicines and Healthcare products Regulatory Agency
MINI	Mini-International Neuropsychiatric Interview
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
NIHR	National Institute for Health Research
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SDS	Sheehan Disability Scale
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
tbc	to be confirmed
tDCS	transcranial direct current stimulation
tDCS AEQ	tDCS Adverse Events Questionnaire
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
YMRS	Young Mania Rating Scale

1 RATIONALE

While there has been some demonstrated efficacy for tDCS as a first-line treatment for depression, the studies to date have investigated tDCS that is provided in the clinic. This is a problem because the treatment requires daily clinic visits for several weeks which could limit its accessibility and uptake among patients. As tDCS is a portable and safe treatment, it could be provided at home.

The present study is a **proof-of-concept trial** to assess the efficacy, acceptability and safety of tDCS treatment for bipolar depression within a community-based setting.

The findings from the present study will be applied to the design of a multi-site, randomised sham-controlled trial of community-based tDCS treatment for bipolar depression.

The present study will also investigate EEG and neuropsychological correlates and potential predictors of clinical response.

1.1 Assessment and management of risk

Noninvasive transcranial direct current stimulation (tDCS) has been used in human for decades. These noninvasive current stimulation techniques use battery-powered current generator devices that have a built-in circuitry to limit the current above a certain level, typically 2 mA.

The most common **adverse events** are mild skin redness (54%) at the site of the electrodes, which resolves following stimulation, itching (39%) and tingling (22%), followed by headache (16%), discomfort (13%) and burning sensation (10%) (Brunoni et al., 2011, Sampaio-Junior et al., 2018). There is no significant difference in rates between active and sham tDCS, except for skin redness which is more common with active (54%) relative to sham tDCS (19%) (Sampaio-Junior et al., 2018). Participants have been unable to distinguish whether they were receiving active or sham tDCS though, and there have been no differences in the discontinuation rates for active and sham treatments, mean rates 10% and 12%, respectively (Meron et al., 2015). In our recent pilot study in unipolar depression, the discontinuation rate has been 7.6% (2 out of 26 enrolled participants).

The **risk of treatment-emergent mania or hypomania** is estimated to be around 4% with a course of active tDCS and 0.5% with sham tDCS, with no statistical difference between active and sham tDCS (Brunoni et al., 2017; Sampaio-Junior et al., 2018). While the rate is lower than the 5-9% risk associated with antidepressant medication, it might be higher than the risk of <1% associated with repetitive transcranial magnetic stimulation (Xia et al., 2008).

Protocols in human trials (≤ 40 min, ≤ 4 milliamperes, ≤ 7.2 Coulombs) have not produced any reports of serious adverse effect or irreversible injury with over 33,200 sessions and 1,000 participants with repeated sessions (Bikson et al., 2016).

2 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

The aim of the present project is to investigate the efficacy, acceptability and safety of community-based tDCS treatment for bipolar depression

2.1 Primary objective

The primary objective is to assess efficacy as measured by clinical response following a course of tDCS treatment.

2.2 Secondary objectives

The secondary objectives are to assess the acceptability and safety of the tDCS sessions.

2.3 Outcome measures/endpoints

Clinical response as measured by clinician-rated MADRS score improvement of >= 50% following the course of tDCS treatment.

2.4 Primary endpoint/outcome

Clinical response as measured by clinician-rated MADRS score improvement of >= 50% following the course of tDCS treatment.

2.5 Secondary endpoints/outcomes

1) Participant retention at the end of the treatment who have completed a minimum of 15 tDCS sessions
2) Participant acceptability questionnaire scales
3) tDCS Adverse Events Questionnaire at each session (Brunoni et al., 2011)

2.6 Exploratory endpoints/outcomes

Exploratory measures:

i. Trained rater measure of depressive symptoms: Montgomery–Åsberg Depression Rating Scale (MADRS) remission rate
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. Self-report Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q)
vii. Self-report acceptability of tDCS from healthy controls.
viii. EEG recordings will be acquired during an eyes-closed resting state for 10 minutes and eyes open resting state for 10 minutes using a mobile EEG device in participants' homes (Muse EEG; https://choosemuse.com/) (Hashemi et al., 2016). Resting state EEG will be acquired at baseline for healthy controls and at 2 timepoints for participants with bipolar depression: 1) at baseline, and 2) at the end of the 6-week course of treatment. EEG coherence, a measure of neural connectivity, will be examined as a potential surrogate outcome measure (Miniussi et al., 2012).
ix. Neuropsychological measures: verbal learning (Rey Auditory Verbal Learning Test (RAVLT)) and information processing speed (Symbol-Digit Modalities Test (SDMT)) will be assessed in participants' homes. Neuropsychological assessments will be delivered to participants and administered by a research team member via video call. Our pilot data indicates feasibility and acceptance of the neuropsychological assessments as all participants had completed the assessments (26 out of 26 participants). The measures will be acquired at baseline for healthy controls, and at 2 timepoints for participants with bipolar depression: 1) at baseline, and 2) at the end of the 6-week course of treatment.

Exploratory outcomes:

1) MADRS score <= 9 following the course of tDCS
2) Improvement in self-reported depressive symptoms as measured by PHQ-9
3) Improvement in anxiety symptoms as measured by HAMA
4) No significant increase in manic symptoms as measured by YMRS score >13
5) Improvement in disability experience as measured by SDS
6) Improvement in quality of life as measured by Q-LES-Q
7) Healthy control participant baseline acceptability questionnaire.
8) We hypothesize that increased functional connectivity in the resting state default mode network is linked with an improvement in depressive symptoms at the end of treatment.
9) We will apply machine learning analysis to examine the potential of resting state EEG coherence to predict clinical response (Al-Kaysi et al., 2016).
10) Effects on cognitive functioning as measured by neuropsychological tasks.

2.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint of evaluation of this outcome measure
Primary Objective To assess the efficacy of tDCS treatment.	Clinical response as measured by MADRS score improvement of >= 50% following the course of tDCS treatment	End of tDCS sessions (visit 21)
Secondary Objectives To assess the acceptability and safety of the intervention	Participant retention at the end of the treatment who have completed a minimum of 15 tDCS sessions Participant acceptability questionnaire scales tDCS Adverse Events Questionnaire	End of tDCS sessions (visit 21) At each session

3 TRIAL DESIGN

The present study is a proof-of-concept trial to assess the efficacy, acceptability and safety of tDCS treatment for bipolar depression within a community-based setting.

4 TRIAL SETTING

School of Psychology, University of East London

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Bipolar depression sample

5.1.1 Inclusion criteria

- participants capable of giving informed consent
- male and female
- minimum of 18 years of age
- diagnosis of bipolar disorder based on DSM-5 criteria, with a current depressive episode of at least a moderate severity
- diagnosis will be confirmed by the Mini-International Neuropsychiatric Interview
- Depressive symptoms severity will be assessed using the Montgomery–Åsberg Depression Rating Scale (MADRS) with a minimum score of 18, indicating at least a moderate severity of symptoms.
- Being on a stable dosage of mood stabilising medication for a minimum of two weeks or not taking any medications for a minimum of two weeks. We would like to emphasize that we would not ask participants to stop their medications in order to take part in the study

5.1.2 Exclusion criteria

- any concurrent psychiatric disorder, including obsessive compulsive disorder
- having a significant risk of suicide
- score greater than 8 in the Young Mania Rating Scale
- 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

5.2 Healthy control sample

5.2.1 Inclusion criteria

- participants capable of giving informed consent
- male and female
- minimum of 18 years of age

5.2.2 Exclusion criteria

- any concurrent psychiatric disorder, including obsessive compulsive disorder
- having a significant risk of suicide
- score greater than 8 in the Young Mania Rating Scale

6 TRIAL PROCEDURES

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

6.1 Recruitment

Based on an effect size of d = 0.70 (Meron et al., 2015; Mutz et al., 2018) following a 6-week course of tDCS treatment (consisting of 15-21 sessions) with 90% power, we will enrol 50 participants to achieve a sample size of 45 participants with bipolar depression who will complete the course of treatment, based on a 10% attrition rate.

We will enrol 35 healthy controls to complete baseline activities.

Our participants have a wide ethnic diversity. In our pilot study, 38% of participants were of non-White ethnicity i.e. 12% Black/African Caribbean, 4% Pakistani, 4% Chinese, 16% Mixed ethnic background, and 62% English or any White background. Recruitment will be from primary care, consulting psychiatrists, print and social media advertisements.

6.1.1 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.

6.1.2 Screening

The screen assessment for participants with bipolar depression requires a DSM-5 diagnosis of major depressive disorder by a MINI interview assessment and a minimum score of 18 on the MADRS. The maximum duration between screening and recruitment is 20 days.

6.1.3 Payment

Participants with bipolar depression will be reimbursed for their participation in the study: $66. (£50. GBP) and for the EEG assessments: $44. (£30. GBP).

Healthy control participants will be reimbursed £20 for their participation in the study.

Participants that travel to the research centre will be reimbursed for their travel expenses, up to a total of £20 per visit.

After the trial, participants will be able to keep the tDCS device if they would like to and will be provided with NICE tDCS for Depression most recent Interventional Procedures Guidance, published 26 August 2015 (https://www.nice.org.uk/guidance/ipg530).

6.2 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

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

6.3 The randomisation scheme: N/A

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

6.4 Blinding: N/A

6.5 Emergency Unblinding: N/A

6.6 Baseline data

The baseline data consist of: MADRS, tDCS AEQ, Acceptability questionnaire, PHQ-9, HAMA, YMRS, SDS, Q-LES-Q, EEG, AVLT, SDMT (Appendix 2).

6.7 Trial assessments

Trial assessments are described in Appendix 2.

6.8 Long term follow-up assessments

Long term follow-up assessments will be acquired at 3 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'.

6.9 Qualitative assessments

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

6.10 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. Should a participant lose capacity to consent during the study then they would be withdrawn from the study, and that their identifiable data already collected with consent would be retained for use, and that no further data collection would take place. Their GP will be informed about their withdrawal, and there will have a telephone follow up at 1 month following their withdrawal.

6.11 Storage and analysis of clinical samples: N/A

6.12 End of trial: N/A

7 TRIAL TREATMENTS

7.1 Name and description of intervention(s) under investigation

We will use the Flow Neuroscience Flow tDCS device (Figure 1). 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.

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

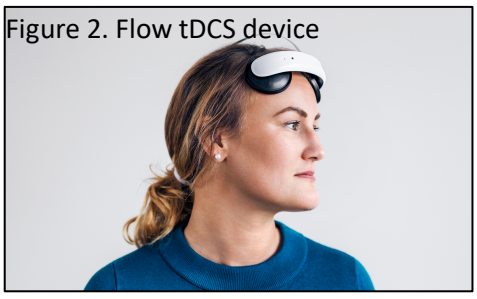


Figure 2. Flow tDCS device

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

7.3 Product Characteristics:

The Flow tDCS device has CE mark approval for the treatment of major depression. The device is portable and commercially available. The device can be programmed to provide the specific stimulation parameters for the study.

The Soterix tDCS device is a similar device which has CE mark approval for the treatment of major depression (Figure 3).

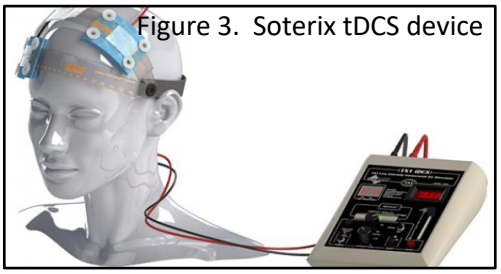


Figure 3. Soterix tDCS device

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

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

7.6 Dosage schedules:

The Flow Neuroscience tDCS headset will be delivered to the participant's home. The device is designed and approved (CE) to be used at home without supervision.

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. Duration of each session is 30 minutes. We will use the Flow Neuroscience tDCS device (Figure 1) with a bifrontal montage: anode at left dorsolateral prefrontal cortex (DLPFC) and cathode at right DLPFC (EEG positions F3 and F4, respectively). Stimulation is 2 mA, and electrode area is 35 cm_2. During each session, participant will be seated comfortably with their eyes open, and research assistant will provide a discreet presence without interacting with the participant by video call.

tDCS parameters are based on meta-analyses (Meron et al., 2015; Dondé et al., 2017; Mutz et al., 2018) indicating that effects are greatest at 2 mA current of 30-minute stimulus. The tDCS equipment records the duration of each session, and there is an automatic shut-off to prevent unsafe use.

7.7 Dosage modifications: N/A

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

7.9 Concomitant medication

Participants who wish to begin another antidepressant treatment while taking part in the study will be able to continue in the trial.

7.10 Trial restrictions

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

7.11 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 the headset. 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.

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

8 RECORDING AND REPORTING OF ADVERSE EVENTS

8.1 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

8.2 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.

8.3 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

8.4 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.

8.5 Notification of deaths

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

8.6 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.

8.7 Overdose: N/A

8.8 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.

8.9 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.

8.10 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.

9 STATISTICAL ANALYSIS PLAN

9.1 Sample size calculation

Based on an effect size of d = 0.70 (Meron et al., 2015; Mutz et al., 2018) following a 6-week course of tDCS treatment (consisting of 15-21 sessions) with 90% power, we will enrol 50 participants to achieve a sample size of 45 participants with bipolar depression who will complete the course of treatment, based on a 10% attrition rate.

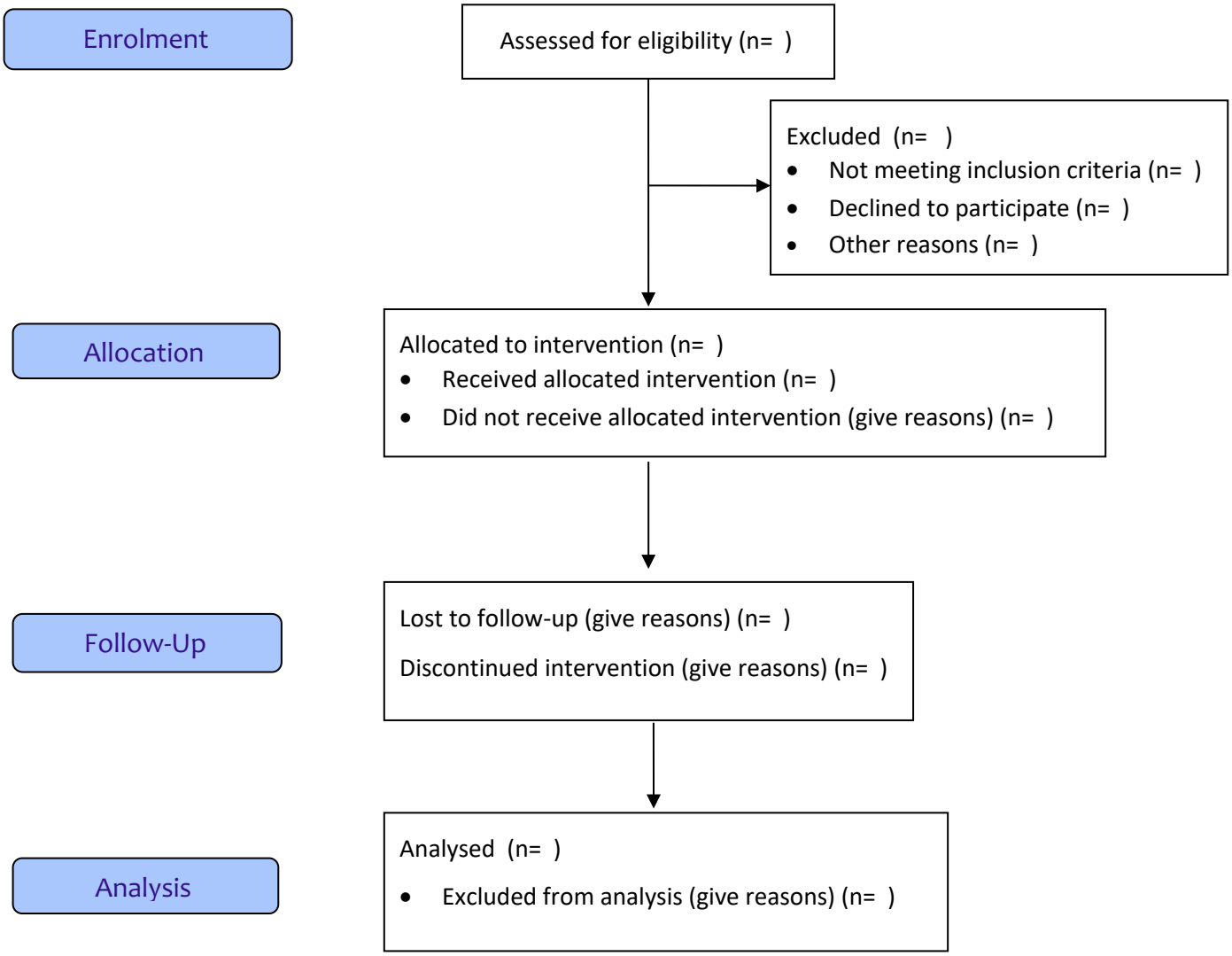
9.2 Planned recruitment rate

The planned recruitment rate is 4-6 participant/s per month.

9.3 Statistical analysis plan

9.3.1 Summary of baseline data and flow of patients

Consort Flow Diagram:



9.3.2 Primary outcome analysis

The primary outcome analysis clinical response which will be measured by the number of enrolled participants who show a clinical response at the end of treatment (MADRS score improvement of >= 50% following the course of tDCS treatment), divided by the total number of enrolled participants, expressed as a percentage.

9.3.3 Secondary outcome analysis

The secondary outcome analyses are; 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; Acceptability, which will be measured by 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, and safety outcomes, which will be measured by calculating the number of severe, moderate and mild adverse events and their relation to the intervention.

9.4 Subgroup analyses: N/A

9.5 Adjusted analysis: N/A

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

9.7 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.

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

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

9.9 Other statistical considerations: N/A

9.10 Economic evaluation: N/A

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11 SCHEDULE OF EVENTS

Study Procedure	Screening	Treatment Period																					Follow up
Visit	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18	V19	V20	V21	V22
Location	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H/T
Week of Treatment	Wk -4 to 0	Wk1	Wk1	Wk1	Wk1	Wk1	Wk2	Wk2	Wk2	Wk2	Wk2	Wk3	Wk3	Wk3	Wk3	Wk3	Wk4	Wk4	Wk5	Wk5	Wk6	Wk6	Wk18
Day of Visit	-20	1	2	3	4	5	8	9	10	11	12	15	16	17	18	19	22	25	29	32	36	39	126
Visit Window (days)	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 14
Screen Information & Consent	x																						
Study Information Sheet		x																					
Inclusion/Exclusion Criteria	x	x																					
Clinical Assessments																							
Demographics	x																						
Height	x																						
Weight	x																						
Clinical Interview	x																						
Pre-existing conditions	x																						
History or treatments	x																						
Concomitant treatments	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
tDCS training session		x																					
tDCS intervention		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Rating Scales																							
MINI	x																						
IQ assessment		x																					
MADRS	x	x									x											x	x
PHQ-9		x									x											x	x
HAMA		x									x											x	x
YMRS		x									x											x	x
SDS		x									x											x	x
Q-LES-Q		x									x											x	x
tDCS Adverse Events Scale		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Acceptability questionnaire		x																				x	x
EEG		x																				x	
Neuropsychological tasks (eg. SDMT, RAVLT,)		x																				x	

Location: Clinic (C), Home (H), Telephone (T)