1 FULL TITLE OF THE TRIAL

Home-based transcranial direct current stimulation in major depressive disorder: a multi-centre, two-parallel group, superiority randomised controlled trial

2 SHORT TRIAL TITLE / ACRONYM

HOME

This protocol has regard for the HRA guidance and order of content.

3 TRIAL IDENTIFIERS

IRAS Number	344318
EudraCT number	
REC Number	
FUNDERS Number	NIHR165425 Health Technology Assessment
Protocol Version Number	1.1
Date	25 September 2025

4 PROTOCOL VERSION HISTORY

Version Number	Date	Protocol Update finalised by (insert name of person):	Reasons for Update
1.0	23 July 2025	Cynthia Fu	Submission to Sponsor
1.1	25 September 2025	Cynthia Fu	1. Section 4. Funding programme name corrected from: “Health Technology Award” to "Health Technology Assessment". 2. Section 5. Statement regarding confidential information removed from the signature page as the protocol will be published by NIHR. 3. Section 9. "National Institute for Health Research" corrected to "National Institute for Health and Care Research". 4. Section 12.7 Added clinician-rated depressive symptom rating scale, HDRS, at week 10 and month 6 to secondary outcomes from clinical monitoring measures. 5. Section 12.7. Added clinician-rated anxiety symptom rating scale, HAMA, at week 10 and month 6 to secondary outcomes from clinical monitoring measures. 6. Section 12.8. Added self-rated measure of depressive symptoms, QIDS-SR, in clinical monitoring measures. 7. Section 12.10. Changed AD-SUS and EQ-5D-5L rating dates from baseline, week 10, months 4, 6 and 9 and early termination, to baseline, week 10 and month 6 only.

			8. Section 19.4. Updated the timepoints for EQ-5D-5L and AD-SUS assessments from 'baseline and 6-month follow up' to baseline, 10 weeks and 6-month follow-up. 9. Section 15.1. Changed inclusion criteria #4 from: "Being antidepressant medication free or taking stable antidepressant medication or being in psychotherapy or not in psychotherapy for at least 6 weeks before enrolment," into two criteria, one for medication and one for psychotherapy, #4: "Either not taking antidepressant medication or taking a stable dose of antidepressant medication for at least 6 weeks before enrolment," and #5: "Either not currently in psychotherapy or engaged in ongoing n psychotherapy for at least 6 weeks before enrolment'. 10. Section 15.1. Changed inclusion criteria #6 from: "Being under the care of GP and / or community mental health services", to: "Being under the care of GP". 11. Section 15.2. Changed exclusion criteria #13 from: "Currently pregnant," to: "If female and of child-bearing potential, currently pregnant or planning to become pregnant during the study". 12. Section 18.1. In Serious Adverse Event (SAE) Definitions, added: "considered significant by the investigator for any other reason", as documented in Section 18.2, Operational definitions. 13. Section 22.11. In Amendments, added "The NIHR will prospectively approve any significant protocol amendments", to confirm that the NIHR would be consulted and would approve any significant amendments.

			14. Section 16.7. Blinding. Removed the following segment of text “by avoiding self-report measures and” which incorrectly stated that we would not use self-report measures. 15. Section 16.16. Description of trial procedures by visit. Edited the blinding status of the junior trial statistician from “blinded” to “Blinded until SAP signed, then unblinded to extract data for DMEC” to enable DMEC reporting. 16. 17.9 Concomitant treatments. Changed from “Concomitant medication” to “Concomitant treatment” to enable capture of all types of concomitant treatments during trial. 17. Section 15.5. Premature Withdrawal Criteria. Edited from “Participants will be withdrawn from the trial if they develop serious adverse effects from any part of the study. Recording of the reasons for withdrawal will be made.“ to “Participants will be withdrawn from the study intervention if they develop serious adverse effects from any part of the study, they will have the option to continue in the trial and recording of the reasons for withdrawal from the study intervention will be made.“ to make it clear that SAEs related to the tDCS intervention will lead to withdrawal of tDCS intervention and optional withdrawal from the trial. 18. Section 13.2.2 Schedule of Events. Edited to include changes made to AD-SUS and EQ-5D-5L recording time points listed in points 7 above. Edited to include QIDS-SR inclusion as listed in point 6 above. 19. Section 7. Funder number added to the study synopsis summary table.

			20. Section 7. All secondary outcomes have been included in the study synopsis summary table. 21. Section 7. Summary of eligibility criteria has been updated in the study synopsis summary table to reflect changes in wording of inclusion criteria. 22. Section 13.2.1. The 'enrolment' section of the CONSORT flow diagram has been updated from 'assessed for eligibility by videoconference' to 'consent for screening and assessed for eligibility'. And 'No significant suicide risk according to CSSRS' and 'No comorbid psychiatric or neurological disorder' have been included here. 23. Section 15.4.2. 'NIHR Clinical Research Networks (CRN)' has been changed to NIHR Research Delivery Network (RDN)' as Clinical Research Networks is the outdated name. 24. Section 19.1. Updated the text to include that that the two-sided t-test will be at the 5% level. 25. Section 19.3. The Statistical analysis plan section has been updated following review from the independent statistician from the TSC.

5 SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
I confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Sponsor:
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..../...../.....
Name (please print):

.....
Position:

.....

Chief Investigator:
Signature: Date:

..../...../.....
Name: (please print):

Cynthia Fu
.....

Statistician:
Signature: Date:

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6 TRIAL KEY CONTACTS

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7 STUDY SYNOPSIS

Trial Title	Home-based transcranial direct current stimulation in major depressive disorder: a multi-centre, two-parallel group, superiority randomised controlled trial	
Short Title	HOME	
Trial Phase	Phase III	
Co-Sponsor	Professor Bashir Al Hashimi Vice President (Research and Innovation) King's College London Tel: 02078487306 Email: vpri@kcl.ac.uk	
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IRAS number	344318	
Funder	National Institute for Health and Care Research (NIHR)	
Funder number	NIHR165425	
Trial Design	Multi-centre, pragmatic, two-parallel group, superiority randomised controlled trial with assessor-blinded / mased outcome assessment	
Trial Participants	Adults aged >= 18 years with DSM-5 major depressive disorder (MDD); current episode at least moderate severity as measured by MADRs >= 18; able to provide informed consent	
Sample size	438	
Treatment duration	10 weeks	
Follow up duration:	6 months	
Extension follow up duration:	9 months	
Trial Objectives and Outcome Measures	Objectives	Outcome Measures

Primary	To evaluate tDCS clinical effectiveness at 10-week end of treatment period between the two treatment arms (treatment as usual (TAU) and TAU plus tDCS) as the difference in clinician-rated depressive symptom severity	Total MADRS
Key Secondary	To evaluate tDCS sustained clinical effectiveness at 6 months between treatment arms as the difference in clinician-rated depressive symptoms	Total MADRS
Secondary #1	To evaluate clinical effectiveness at 10-week end of treatment period between treatment arms as the difference in self-rated depressive symptoms	Total MADRS-S
Secondary #2	To evaluate clinical effectiveness at 10-week end of treatment period between treatment arms as the difference in clinician-rated depressive symptoms	Total HDRS
Secondary #3	To evaluate anxiety symptoms at 10-week end of treatment period between treatment arms as the difference in clinician-rated anxiety symptoms	Total HAMA
Secondary #4	To evaluate treatment response at 10-week end of treatment period between treatment arms	Participants >= 50% improvement MADRS rating
Secondary #5	To evaluate treatment remission at 10-week end of treatment period between treatment arms	Participants <=10 MADRS rating
Secondary #6	To evaluate sustained clinical effectiveness at 6 months between treatment arms as the difference in self-rated depressive symptoms	Total MADRS-S
Secondary #7	To evaluate sustained clinical effectiveness at 6 months between treatment arms as the difference in clinician-rated depressive symptoms	Total HDRS

Secondary #8	To evaluate sustained anxiety symptoms at 6 months between treatment arms as the difference in clinician-rated anxiety symptoms	Total HAMA
Secondary #9	To evaluate sustained treatment response at 6 months between treatment arms	Participants >= 50% improvement MADRS rating
Secondary #10	To evaluate sustained treatment remission at 6 months between treatment arms	Participants <=10 MADRS rating
Summary of eligibility criteria	Aged 18 or over at study entry Diagnosis of major depressive disorder, with at least moderate severity of depressive symptoms Either not taking antidepressant or taking a stable dose of antidepressant medication for at least 6 weeks before enrolment. Either not currently in psychotherapy or in ongoing psychotherapy for at least 6 weeks before enrolment Being under the care of GP Agreeable for GP to be regularly informed about study participation Able to provide written, informed consent No significant suicide risk No primary comorbid psychiatric disorder Not using (daily) medications that affect cortical excitability No current illicit drug use or heavy alcohol use No history of brain stimulation, esketamine/ ketamine, or psychosurgery for the treatment of depression No current medical disorder or neurological disorder that may mimic mood disorder No cognitive impairment, implant in the brain or neurocranial defect, shrapnel or any ferromagnetic material in the head, nor any active implantable medical device Not currently pregnant or planning to become pregnant during the trial; No concurrent enrolment in another interventional study	
Intervention:	transcranial direct current stimulation (tDCS) intervention: 5 sessions per week for 3 weeks followed by 3 sessions per week for 7 weeks, for a total of 36 sessions in 10 weeks. tDCS device is headset with bifrontal montage, anode at left dorsolateral prefrontal cortex (DLPFC) and cathode at right DLPFC (EEG positions F3 and F4, respectively). Stimulation is 2 mA for 30 minutes with a gradual ramp up over 30 seconds. Electrode area is 23 cm^2.	

Comparator Intervention:	Treatment as usual (TAU) intervention: standard care, such as psychotherapy and/or antidepressant medication or no treatment, as decided by participant and treating clinician.
Planned trial sites	Cardiff and Vale Health Board (CAVUHB) Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (CNTW) Northamptonshire Healthcare NHS Foundation Trust (NHFT) Nottinghamshire Healthcare NHS Foundation Trust (NOTTS) South London and Maudsley NHS Foundation Trust (SLaM) Hampshire and Isle of Wight Healthcare NHS Foundation Trust (HIOWH)

8 INVESTIGATIONAL DEVICE DETAILS

Device Name	Flow FL-100
Manufacturer Name	Flow Neuroscience
Principle intended use	To administer tDCS intervention
Is the device CE marked and used within its purpose?	Yes
Is the device currently used within the department?	No

9 LIST OF ABBREVIATIONS

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
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
MADRS-S	Montgomery–Åsberg Depression Rating Scale-self report
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 and Care Research
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control

QIDS-SR	Quick Inventory of Depressive Symptomatology Self Report
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
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

10 CONTENTS

11 BACKGROUND & RATIONALE

11.1 What is the problem being addressed?

MDD is prevalent, a leading cause of years lost to disability, and is the main precursor to suicide (WHO, 2017). Since the COVID-19 pandemic, there has been a marked increase in rates in the UK to 1 in 5 people, which has been even higher in women, younger adults and in people living in regions of high deprivation (ONS, 2021).

The National Institute for Health and Care Excellence (NICE) recommends antidepressant medication and psychotherapy as first line treatments (NG222) (NICE, 2022). However, over a third of patients do not achieve clinical remission, despite a full treatment trial with either modality (Thomas et al., 2013; Cipriani et al., 2018). Antidepressant medications have adverse effects, such as weight gain, tremors, somnolence and sexual dysfunction, which impair compliance and outcomes (Rush et al., 2006; Saha et al., 2021). Less than half of patients enrolled in the Improving Access to Psychological Therapies (IAPT) programme complete a course of psychotherapy (NHS, 2022), and patient preference markedly affects treatment satisfaction, adherence and positive outcomes (Tringale et al., 2022).

Our patient and public involvement (PPI) members have emphasised the importance of a wider choice of treatments to address the limited efficacy, tolerability and patient acceptability of existing treatment options.

11.2 What is transcranial direct current stimulation (tDCS)?

tDCS is a form of non-invasive brain stimulation that applies a weak (0.5-2 mA) direct electrical current via scalp located electrodes (Meron et al., 2015; Mutz et al., 2018, 2019; Woodham et al., 2021). It modulates neuronal membrane potential thresholds, facilitating action potential discharge, but does not directly trigger action potential, in contrast to repetitive transcranial magnetic stimulation (rTMS), nor does it cause a seizure, in contrast to electroconvulsive treatment (ECT).

tDCS is applied through rubber electrodes in a headband worn over the forehead or in a flexible cap. The anode is typically positioned over the left dorsolateral prefrontal cortex (DLPFC) and cathode over the right DLPFC, suborbital or frontotemporal region (Woodham et al., 2021). Modulation of DLPFC activity within the neural network underlying MDD is a key mechanism for efficacy across different treatment modalities, including medication, psychotherapy and brain stimulation (Ma, 2015; Woodham et al., 2021).

tDCS is a novel treatment with evidence of efficacy, safety and acceptability in MDD (Woodham et al., 2021, 2022, 2023; Rimmer et al., 2024). We have shown that tDCS can be delivered safely by the patient themselves in their own home with remote supervision, leading to an increased remission rate relative to sham tDCS (Woodham et al., 2024). tDCS can be used on its own or combined with antidepressants or psychotherapy (Meron et al., 2015; Mutz et al., 2018, 2019; Woodham et al., 2022, 2024; Ghazi-Noori et al., 2024). Our PPI members have been

strongly positive about
tDCS due to its potential efficacy, safety, innovation, acceptability and through being home-based.

11.3 What do we know: review of published evidence and ongoing research

From an individual patient data meta-analysis, active relative to sham tDCS showed significant improvement in depressive symptoms (effect size 0.31, 95% confidence interval (CI) 0.15 to 0.47, $P < 0.01$), clinical response (30.9% vs. 18.9%, respectively; odds ratio (OR) 1.96, $P < 0.01$) and clinical remission (19.9% vs. 11.7%, respectively; OR = 1.94, $P < 0.01$) in 572 MDD participants from 9 studies (Moffa et al., 2020). Ours and others meta-analyses have found high efficacy with no significant differences in attrition or adverse events between active and sham groups (meta-analyses: Mutz et al., 2018, 2019; Moffa et al., 2020).

A course of tDCS treatment requires daily sessions for several weeks. Previous studies had been conducted in research settings and required daily commutes to ensure that treatment can be supervised (Mutz et al., 2018, 2019; Moffa et al., 2020). However, daily clinic visits would be difficult for many patients and costly for the NHS.

Figure 1.

Figure 2.

As tDCS is portable and safe, we have developed and tested a home-based program with real-time remote supervision by video conference (Woodham et al., 2022, 2024; Ghazi-Noori et al., 2024). We have used two tDCS devices: Neuroelectrics StarStim tDCS device (Figure 1) and Flow Neuroscience Flow tDCS device (Figure 2). The StarStim tDCS device is a flexible neoprene cap with electrodes fitted in, and there are different cap sizes (small, medium, large) for different head sizes. The Flow tDCS device is an adjustable headset with the electrodes built in. In our open-label study, we found high acceptability and feasibility (Woodham et al., 2022), and our qualitative analysis found that participants preferred having sessions at home and would recommend tDCS (Rimmer et al., 2024).

Following on our open-label study, we completed a Phase II fully remote, multisite, double-blind, placebo-controlled, superiority randomised controlled trial of home-based active vs. sham tDCS treatment in MDD (clinicaltrials.gov NCT05202119) (Woodham et al., 2024). Participants were 174 MDD individuals, with at least a moderate severity of depressive symptoms, as measured by 17-item Hamilton Depression Rating Scale (HDRS) score >=16, and were either treatment free or taking antidepressant treatment or in psychotherapy. Participants were randomised to either active (n=87; mean age 37.1 years, standard deviation (SD) 11.1) or sham treatment (n=87; mean age 38.3 years, SD 10.9).

The anode was positioned over left DLPFC, EEG position F3, and cathode over right DLPFC, EEG position F4, based on international 10/20 EEG positions. Each session was 30 minutes. Active tDCS current was 2 mA. Sham tDCS current was 0 mA with brief ramp up and ramp down at start and end of the session to mimic tingling sensation in active tDCS.

Treatment lasted for 10
weeks, consisting of 5 sessions per week for 3 weeks then 3 sessions per week for 7 weeks, and was followed by a 10-week open-label phase, consisting of active tDCS sessions for all participants. The primary outcome was the effect of active relative to sham tDCS on depressive symptoms at the 10-week end of treatment as measured by HDRS.

The trial pre-registered primary outcome was the difference between groups (active tDCS and sham tDCS) in HDRS score change at 10 weeks. Significant improvements were found in the active group (mean improvement 9.4 points (SD = 6.3)) as compared to the sham group (mean improvement 7.1 points (SD = 6.1)) (95% CI 0.5 to 4.0, p = 0.01).

Positive treatment effects were consistently observed across several secondary outcomes. Significant improvements in clinician-rated depressive symptoms were found in the active group (mean improvement 11.3 points, SD 8.8) as compared to sham group (mean improvement 7.7 points, SD 8.5) (95% CI 1.1 to 6.1, p = 0.006) as measured by the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Significant improvements in self-rated depressive symptoms were found in the active group (mean improvement 9.9 points (SD 8.9)) as compared to sham group (mean improvement 6.2 points (SD 9.1) (95% CI 0.9 to 6.4, p = 0.009) as measured by the MADRS-Self report version (Svanborg and Åsberg, 1994).

In clinical response, there was a significantly greater response rate in active (54.4%) as compared to sham group (26.9%) (odds ratio (OR) 3.25, p = 0.001) as measured by 50% greater improvement in HDRS score from baseline, as well as in response rate as measured in MADRS score, active group response rate (63.0%) relative to sham group (31.6%) (OR 3.70, p < 0.001). In clinical remission, there was a significantly greater remission rate in active (44.9%) as compared to sham group (21.8%) (OR 2.93, p = 0.004) as measured by HDRS score less than 8, and as measured by MADRS score less than 10, remission rate in active (57.5%) as compared to sham group (29.4%) (OR 3.26, p = 0.002).

The overall discontinuation rate was 15.4% (n = 25 participants), with no significant differences between the active (n=13) and sham (n=12) groups indicating similar tolerability for both treatments (Woodham et al., 2024). The most common side effects are 'burning' sensations (16.2%), skin redness (12.3%), scalp pain (10.1%), itching (6.7%), and tingling (6.3%) (Chhabra et al., 2020), in which active tDCS was associated with more skin redness (p < 0.001) and skin irritation (p = 0.05) as compared to sham tDCS which improved following the session, while there were no differences in headache, neck pain, scalp pain, itching or burning sensation (Woodham et al., 2024).

From qualitative analyses of individual interviews, participants described that they liked having the sessions at home and they would recommend tDCS treatment (Rimmer et al., 2022; Woodham et al., 2024). Moreover, participants in NHS primary care services as well as secondary care community mental health services described the tDCS device as easy to use, convenient as it fit into their routine, that they felt they were taking control of the treatment and how it provided an alternative to previous ineffective treatments (Griffiths et al., 2023, 2024).

Meta-analyses and our trial demonstrate efficacy for home-based tDCS treatment and qualitative analyses of individual interviews show high acceptability, enthusiasm and need for more treatment options. However, we do not know the clinical and cost-effectiveness in real world care settings. To address the evidence gap, we propose a multi-site pragmatic trial to establish effectiveness and cost-effectiveness in NHS care pathways.

11.4 Rationale

MDD is an urgent and growing challenge. Mental ill health remains the most significant cause of disability in the UK, costing approximately £118 billion annually or 5 per cent of GDP (WHO, 2017; McDaid et al., 2022). Since the COVID-19 pandemic, depression prevalence has doubled to 1 in 5 people, up from 1 in 10 (ONS, 2021). Particularly concerning are higher rates in young women aged 16 to 29 years, around 1 in 3 young women, and in the most deprived areas, around 1 in 4 adults, which is double the rate in the least deprived areas (ONS, 2021).

Furthermore, treatment resistant depression (TRD) is prevalent in the UK. It is estimated that 55% of MDD patients meet the National Institute of Health Research (NIHR) Health Technology Assessment (HTA)-funded CoBAIT (Wiles et al., 2014) and MIR (Kessler et al., 2018) trials' TRD definition as having persistent depressive symptoms following an adequate dose of antidepressant medication for 6 weeks, as measured by a score of 14 or more in the self-report Beck Depression Inventory (Beck et al., 1996). Based on this definition, the majority of the sample in our efficacy trial had of TRD (n=109 out of 174 MDD participants, 63%) with persistent depressive symptoms of at least moderate severity despite a 6-week trial of antidepressant medication for their current episode and were still taking medication (Woodham et al., 2024). Participants with TRD will be included in the present trial.

Given these findings, there is a pressing need for a pragmatic efficacy and cost-effectiveness RCT for remotely-supervised home-based tDCS within NHS care pathways, both as a first-line and further-line non-pharmacological treatment option. We have assembled a team with the expertise and capabilities to successfully conduct this trial and ensure its outcomes are impactful and implemented within care pathways.

12 TRIAL OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Aim: To evaluate clinical-effectiveness and cost-effectiveness of home-based tDCS treatment for MDD.

12.1 Primary Objective

To evaluate clinical effectiveness as the difference in depressive symptom severity as measured by the clinician-rated MADRS at the 10-week end of treatment between the two treatment arms: those receiving treatment as usual (TAU) and those receiving TAU plus tDCS.

12.2 Key secondary objective

To evaluate sustained clinical effectiveness as the difference in depressive symptoms as measured by MADRS at the 6-month follow up between the two treatment arms.

12.3 Additional secondary objectives

To assess further clinical outcomes at 10-week end of treatment and at 6-month follow up.

12.4 Outcome measures/endpoints

Outcome measures are assessed at 10-week end of treatment and at 6-month follow up.

12.5 Primary endpoint/outcome

Depressive symptom severity as measured by clinician rated MADRS from baseline to week 10.

12.6 Key secondary endpoint/outcome

Depressive symptom severity as measured by clinician rated MADRS from baseline to month 6.

12.7 Additional secondary endpoints/outcomes

The following outcome measures are assessed at week 10 and month 6:

1) Self-rated depressive symptoms: total score in MADRS-self report version (MADRS-S)
2) Clinician-rated depressive symptoms: total score in 17-item Hamilton Depression Rating Scale (HDRS)
3) Clinician-rated anxiety symptoms: total score in Hamilton Anxiety Rating Scala (HAMA)
4) Clinician-rated response: number of participants achieving >= 50% improvement in MADRS score
5) Clinician-rated remission: number of participants achieving <= 10 in MADRS score.

12.8 Clinical monitoring measures

1) Self-rated depressive symptoms: MADRS-S at 1, 4, 7 weeks, 4 and 9 months
2) Self-rated depressive symptoms: QIDS-SR at 1, 4, 7, 10 weeks, 4, 6 and 9 months
3) Clinician-rated depressive symptoms: HDRS at 1, 4, 7 weeks, 4 and 9 months
4) Clinician-rated anxiety symptoms: HAMA at 1, 4, 7 weeks, 4 and 9 months
5) Clinician-rated response: >= 50% improvement in MADRS score at 4 and 9 months
6) Clinician-rated remission: <=10 in MADRS score at 4 and 9 months

12.9 Quality of life and safety measures

1) Quality of life: measured by EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) (Feng et al., 2021) at 10 weeks and 6 months.
2) Safety: Clinician-rated manic symptoms, measured by Young Mania Rating Scale (YMRS) (Young et al., 1978) at 1, 4, 7, 10 weeks, 4, 6 and 9 months.
3) Safety: Adverse events, measured by tDCS Adverse Events Questionnaire (AEQ) (Brunoni et al., 2011) at 1, 4, 7, 10 weeks, 4, 6 and 9 months.

12.10 Health economics measures

1) Quality-adjusted life-years (QALY) will be determined based on EQ-5D-5L at 10 weeks and 6 months
2) Health and social care costs will be measured using the Adult Service Use Schedule (AD-SUS) (Strauss et al., 2023) and clinical records at 10 weeks and 6 months
3) Incremental cost-effectiveness between TAU and TAU+tDCS treatment arms measured by cost per QALY at 10 weeks and 6 months

12.11 Process evaluation and implementation work

The following process measures will be taken for tDCS group to describe the treatment experience.

1) Adherence to tDCS sessions based on number of participants completing at least 60% sessions (21 sessions) at 10 weeks
2) Discontinuation rates before 10 weeks
3) Acceptability: measured by Treatment Acceptability Questionnaire (TAQ) and qualitative interviews (Woodham et al., 2022, 2025)
4) Fidelity: we will produce records and evaluate fidelity in a random sample of treatment sessions, using a delivery fidelity checklist based on the intervention training manual.
5) Implementation: interviews with participants and professionals to explore challenges to implementation, and we will create a network of stakeholders to consider trial results and to produce recommendations for wider rollout.

12.12 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint of evaluation of this outcome measure

Primary Objective To evaluate clinical effectiveness as the difference in depressive severity at 10-week end of treatment between the two treatment arms: those receiving treatment as usual (TAU) alone and those receiving TAU plus tDCS.	Depressive symptoms as measured by clinician-rated MADRS at 10 weeks.	10-week end of treatment
Key Secondary Objective To evaluate clinical effectiveness at 6-month follow up as measured by difference in depressive symptoms between treatment arms	Depressive symptoms as measured by clinician-rated MADRS at 6-month follow up.	6-month follow up
Additional Secondary Objectives To further evaluate clinical effectiveness in terms of: Self-rated depressive symptoms Clinician-rated depressive symptoms Clinician-rated anxiety symptoms Clinician-rated response Clinician-rated remission	 Total MADRS-S rating Total HDRS rating Total HAMA rating Participants >= 50% improvement MADRS rating Participants <=10 MADRS rating	All timepoints are at: 10-week end of treatment and 6-month follow up

13 TRIAL DESIGN & FLOWCHART

The trial design is multi-centre, pragmatic, two-parallel group, superiority RCT of TAU and TAU + tDCS for the treatment of major depression, with masked outcome assessment within a community-based setting.

13.1 Study phases

13.1.1 Treatment phase

Participants will be randomised into one of the two arms: treatment as usual (TAU) or TAU plus tDCS for 10 weeks. Participants will be aware of the treatment arm to which they have been allocated.

13.1.2 Follow up phase

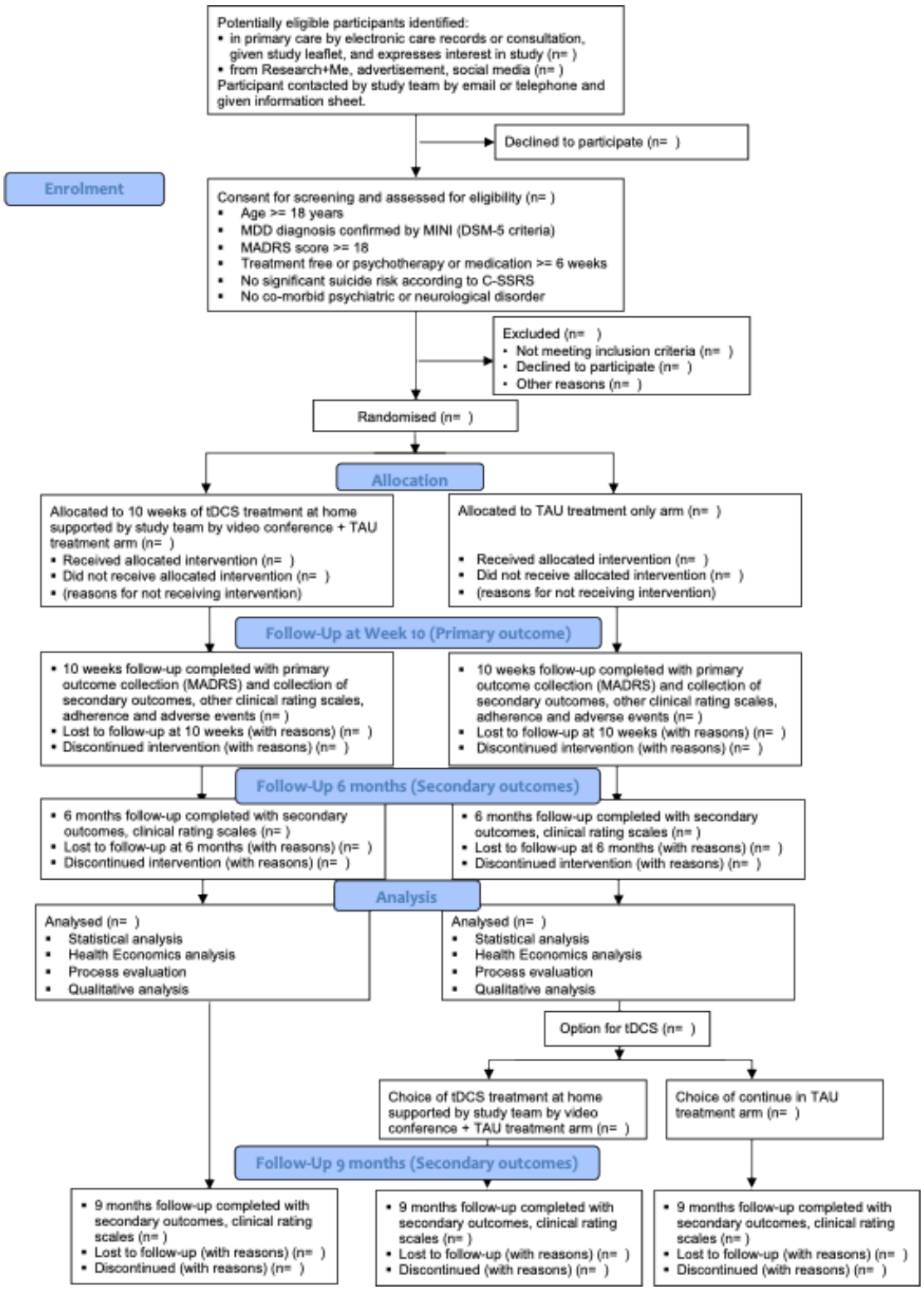
Ongoing follow up will be continued for 6 months. Participants in the tDCS+TAU group are able to keep the tDCS devices and to continue with stimulations if they would like to. The research team will continue to have access to see the number of stimulations that are completed during this phase.

13.1.3 Extension follow up phase

After the 6-month follow up visit, participants in the TAU treatment arm will be given the option to receive the tDCS treatment in addition to ongoing TAU or to continue with TAU until the 9-month visit. Participants who choose to receive the tDCS treatment+TAU will have an additional study visit with the research team member who will show them how to use the tDCS device and will be present for their first tDCS treatment session. Participants will be able to complete 5 sessions of tDCS for 3 weeks, and then 3 sessions per week for 7 weeks. If they wish to discuss adverse events with the study team during the 10 weeks of self-selected tDCS treatment, participants will be able to arrange an unscheduled study visit to discuss any issues with the research assistant.

13.2 Trial Flow Chart

13.2.1 CONSORT Flow Diagram



13.2.2 Schedule of Events

Study Procedure	Enrolment	Baseline	Treatment Period					Follow up		Extension Follow up	Early termination
Timepoint		T0	T1	T2	T3	T4	T5	T6	T7	T8	TET
Visit	V-1	V0	V1	V2	V3	V4	V5	V6	V7	V8	VET
Week/month of treatment	w-3 to 0	w0	w0	w1	w4	w7	w10	m4	m6	m9	w1 – m9
Location	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H	C/H
Visit Window (days)	± 5		± 7	± 5	± 5	± 5	± 5	± 7	± 7	± 14	-
Informed Consent	X										
Screen Assessment	X										
Sociodemographics	X	X									
Clinical Interview	X										
Randomisation / allocation (1)		X									
tDCS device ordering		X									
tDCS training (2)			X						X		
Initial tDCS stimulation (2)			X						X		
MINI	X										
MADRS	X	X		X	X	X	X	X	X	X	X
MADRS-S (3)		X		X	X	X	X	X	X	X	X
HDRS		X		X	X	X	X	X	X	X	X
HAMA		X		X	X	X	X	X	X	X	X
QIDS-SR (3)		X		X	X	X	X	X	X	X	X
C-SSRS	X	X		X	X	X	X	X	X	X	X
YMRS	X	X		X	X	X	X	X	X	X	X
AEQ	X	X	X	X	X	X	X	X	X	X	X
AUDIT-C	X										
EQ-5D-5L		X					X		X		
AD-SUS		X					X		X		
TAQ		X					X	X	X	X	X
Qualitative Interviews		X					X			X	X
Review Concomitant medications/treatments	X	X	X	X	X	X	X	X	X	X	X
Safety assessment / Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X

1. Randomisation will be completed after all baseline assessments have been completed. The intervention will be shipped to participants allocated to TAU + tDCS after randomisation.
2. TAU + tDCS treatment arm: research team member will meet with participants to provide tDCS training and will be present for first tDCS session.
3. Participants will self-report for MADRS-S and QIDS-SR rating scale.
4. Extension follow up phase: for participants who choose TAU + tDCS, training visit will be scheduled after tDCS device has been posted to participant.

14 TRIAL SETTING

The study will take place in the community. All participants will receive the treatment at home. Participants will be recruited from primary care and community mental health services, and participants can also self-refer from advertisements and social media. Assessments and interventions will take place in participants' homes by video conference or at the research sites if this is preferred by the participant.

Research sites:

- Cardiff and Vale Health Board (CAVUHB)
- Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (CNTW)
- Northamptonshire Healthcare NHS Foundation Trust (NHFT) and Northamptonshire NHS primary care providers
- Nottinghamshire Healthcare NHS Foundation Trust (NOTTS)
- South London and Maudsley NHS Foundation Trust (SLaM)
- Hampshire and Isle of Wight Healthcare NHS Foundation Trust (HIOWH)

15 SELECTION & WITHDRAWAL OF PARTICIPANTS

15.1 Inclusion criteria (all to be satisfied)

1) Adults aged 18 years or over
2) Current episode of depression based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria (APA, 2013) for major depressive disorder (MDD) as assessed by structured clinical assessment, Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998)
3) Having at least a moderate severity of depressive symptoms as measured by a score of at least 18 in MADRS
4) Either not taking antidepressant medication or taking a stable dose of antidepressant medication for at least 6 weeks before enrolment.
5) Either not currently in psychotherapy or in ongoing psychotherapy for at least 6 weeks before enrolment.
6) Being under the care of GP
7) Agreeable for GP to be regularly informed about study participation
8) Able to provide written, informed consent

15.2 Exclusion criteria

1) Significant suicide risk as measured by answering 'yes' to questions 4, 5 or 6 on the Columbia Suicide Severity Rating Scale (C-SSRS) Screen (Posner et al., 2011)
2) Primary comorbid psychiatric disorder (e.g. obsessive compulsive disorder) based on DSM-5 criteria as assessed in MINI
3) Current daily use of medications that affect cortical excitability (e.g. benzodiazepines)
4) Current illicit drug use or heavy alcohol use with high risk of alcohol use disorder as measured by a score of $\geq$ 5 in Alcohol use disorders identification test consumption (AUDIT C) (Khadjesari et al., 2017; NICE, 2023)

5) History of electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), cranial electrotherapy stimulation (CES), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), or other brain stimulation
6) History of esketamine / ketamine for treatment of depression
7) History of psychosurgery for depression
8) Having cognitive impairment (e.g. dementia)
9) Current medical disorder or neurological disorder that may mimic mood disorder (e.g. hormonal disorder, unstable heart disease)
10) Have any implant in the brain or neurocranial defect
11) Have shrapnel or any ferromagnetic material in the head
12) Have any active implantable medical device (e.g. pacemaker)
13) If female and of child-bearing potential, currently pregnant or planning to become pregnant during the study
14) Concurrent enrolment in another interventional study

15.3 Eligibility criteria: clinician qualitative interviews for implementation

Clinicians (e.g. psychiatrist, nurse, psychologist, occupational therapist, GP, or allied professional) who are involved in the treatment of patients with MDD.

15.4 Selection of Participants

15.4.1 Recruitment

We will keep detailed records about eligible referrals, enrolments, intervention adherence and early discontinuations. We will document this in the CONSORT flow diagram.

Anonymised information who are not randomised will include for CONSORT reporting: age, gender, ethnicity, and the reason not eligible for trial participation or if they are eligible but declined.

To monitor intervention adherence, we will measure tDCS device use in real-time for each participant.

We are including a 6-month Internal Pilot RCT to assess recruitment and retention feasibility. We plan that each site can recruit 4 participants per month. The progression criteria are: Green 100% total number of participants recruited (n=144); Amber 51-99% (n=73-143); Red 50% (n=72).

For early discontinuation, we will contact participants for a final interview for an assessment of clinical measures, adverse events, acceptability, and qualitative interviews.

15.4.2 Participant identification

We will recruit from 6 mental health centres, located throughout the UK: Cardiff and Vale Health Board (CAVUHB); Cumbria, Northumberland, Tyne and Wear NHS Foundation Trust (CNTW); Northamptonshire Healthcare NHS Foundation Trust (NHFT)/Northamptonshire NHS primary care providers; Nottinghamshire Healthcare

NHS Foundation Trust
(NOTTS); South London and Maudsley NHS Foundation Trust (SLaM); and Hampshire and Isle of Wight Healthcare NHS Foundation Trust (HIOWH).

Participants will be recruited through a dedicated website, registry, social media, and NIHR Research Delivery Network (RDN) to identify primary care practices. We will continue to recruit through the online registries: NIHR Be Part of Research, Call for Participants and MQ Participate. We will explore recruitment support through NHS DigiTrials, Facebook and Instagram.

The study will be listed publicly on the South London and Maudsley NHS Trust 'Take Part in Research' webpage: https://slam.nhs.uk/take-part-in-research.

The Research+Me recruitment platform (www.researchplusme.co.uk), which is linked to a high intensity social media campaign, together with the NIHR Be Part of Research registry, which has 6,691 volunteers who have stated an interest in depression and living within 20 miles of our recruitment centres. Research+Me is an NHS-owned recruitment platform developed to empower patients and healthy volunteers to access research. The platform has approval from the Health Research Authority Research Ethics Committee (REC 23/NE/0090), has a robust infrastructure and governance protocols and an excellent track record. Participants are able to register their interest and provide initial demographic and clinical information. Currently, about 3,000 volunteers are registered with depression on Research+Me. The social media campaign can deliver focused messages based on recruitment inclusion criteria, e.g. 'suitable for people who are taking medication but are still feeling low' and will use promotions that engage a diverse population. The social media has a reach of about 2.4 million people, and we estimate that about 10% will respond. The online pre-screening identifies potentially eligible participants, and postcode tagging allows participants to be connected with their nearest recruiting centre. Research+Me platform has been successfully used in NIHR HTA-funded trials (ASCEnD), commercial trials (RELIEVE-IBSD, RADIAL), and has been allocated funding by the UK Mental Health Mission to create a registry for clinical trials in mood disorders.

Participants who self-refer to be part of the research via the above methods will be contacted by a research team member to review the main inclusion and exclusion criteria. If they appear to meet the criteria, the participant information sheet (PIS) will be provided to the participant and the screening interview will be arranged.
We will follow the NIHR INCLUDE Ethnicity Framework (trialforge.org), and our sites are nationally representative across the UK in urban and rural areas. People living in deprived neighbourhoods in England and Wales are more likely to be from an ethnic minority background(https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/people-living-in-deprived-neighbourhoods/latest/). We will actively engage with local community organisations to ensure recruitment from wide ethnic diversity and socioeconomic status. We will recruit from GP practices based in postcodes in areas of high deprivation (http://dclgapps.communities.gov.uk/imd/iod_index.html). Index of multiple deprivation (IMD) is a measure of relative deprivation, ranging from: (1) most deprived decile to (10) least deprived decile, which encompasses a wide range of components based on income, employment, education, health, crime, living

environment. The IMD is summarised in local authority postcode maps, and we will obtain deprivation data based on participant's postcode (CDRC, 2024).

Only a member of the patient's existing clinical care team or a member of the research delivery network 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 registered with a GP for study participation.

For the qualitative interviews with 20 clinicians: Referrers, including GPs and community mental health teams, will be approached to take part in the qualitative interviews for implementation.

15.5 Criteria for Premature Withdrawal

Participants will be withdrawn from the study intervention if they develop serious adverse effects from any part of the study, they will have the option to continue in the trial and recording of the reasons for withdrawal from the study intervention 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 they will have a telephone follow up at 1 month following their withdrawal.

16 TRIAL PROCEDURES

The Schedule of Events is presented in table format in section 13.2.2.

16.1 Informed Consent Procedures

The Chief Investigator (CI) for multicentre studies retains overall responsibility for the conduct of research which includes the taking of informed consent of participants at their site. The local sites each have a locally employed Principal Investigator (PI) that overseas their team and consent for their patients at their individual 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 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 is 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

The informed consent form can be signed manually on paper for participants who choose to attend the research centre. For participants who choose remote study visits, the informed consent form will be signed by the participant and the researcher during the videoconference call electronically, using DocuSign or Adobe Sign, which are software which records the time and date of the signature and is authenticated in the software system.

To comply with the Welsh Language Act 1993, the Participant Information Sheets and Consent forms will be translated into Welsh and provided where this is requested by a participant at a research site.

16.2 Risks/burdens

Noninvasive transcranial direct current stimulation (tDCS) has been used in humans 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).

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). Concerns about safeguarding or clinical risk will be discussed with the CI, trial manager, and the local PI. Adverse events are reviewed at each study visit and recorded in the case report forms, and participants can contact research team members at any time on a dedicated study mobile phone number which is held by the CI. Participants may choose to withdraw from the study for any reason which will not impact on their care. All research team members will have training on reviewing, recording and reporting of adverse events and serious adverse events.

16.3 Screening

Participants will be contacted initially by email with some of the inclusion and exclusion criteria to determine potential eligibility. They will then engage in a short telephone screen prior to the formal screening assessment.

The screen assessment for participants with major depressive disorder 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 enrolment s 24 days (3 weeks +/- 3 days).

Data that will be collected at the screening visit:

1) Socio-demographic data: age, gender, sex at birth (optional), ethnicity, marital status, level of education, current occupation, IMD as measured by postcode
2) Clinical data: duration of current treatment, duration of current episode, past psychiatric history, including previous treatments, initial onset of depression, number of previous episodes, hospital admissions, history of self harm and suicide attempts; and past medical history.
3) Clinical diagnosis: MINI
4) Clinical symptom severity: MADRS, YMRS
5) Suicide risk: C-SSRS
6) Adverse events: AEQ
7) AUDIT-C

16.4 Payment

We will reimburse participants by vouchers for each visit. Participants will be reimbursed £20 in vouchers for each of the following study visits after randomisation: Baseline, weeks 1, 4, 7, 10 and months 4, 6 and 9.

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

After the trial, participants will be able to keep the tDCS device if they would like to. Participants will not be reimbursed for attending the screening visit.

16.5 The randomisation scheme:

Following written consent, confirmation of eligibility to participate in the trial and baseline assessment participants will be randomly allocated to either treatment as usual (TAU) or TAU+tDCS in a 1:1 ratio. Randomisation will be at the participant level, stratified by recruitment site, using randomly varying block sizes within site.

16.6 Method of implementing the randomisation/allocation sequence:

Randomisation will be implemented via an online system provided by King's College London (KCL) Clinical Trial Unit (KCTU). This bespoke 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.

Randomisation will be at the level of the individual and the system will employ block randomisation with randomly varying block sizes and will be stratified by site. The details needed for randomisation (study site, date of birth (dd/mm/yyyy), initials and unique patient identity number)) will be held in a dedicated database. Research assistants, senior trial manager, project coordinator, PIs and CI will have access to the randomisation system. Randomisation will be undertaken by research assistants, senior trial manager, project coordinator and CI onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system. Research assistants will have access to randomise participants at the research site where they are based. Research assistants at KCL, senior trial manager, project coordinator and CI will have access to randomise participants at all research sites.

Participants will be informed of their group assignment by telephone by the research assistant who will be conducting their study visits for the duration of the trial (this research assistant will not be blinded to treatment group) and a tDCS device will be ordered for those who have been assigned to the TAU+tDCS treatment arm.

16.6.1 Security

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 date of birth will be entered on the randomisation system. Whereas NHS number, email addresses, participant names and 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.

16.6.2 Data Quality Processes

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst where appropriate for the purpose of data cleaning. 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.

16.6.3 Database Lock

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.

16.7 Blinding

For this pragmatic effectiveness RCT and following consultation with KCTU and KCL Research Design Service, we have opted for a TAU comparator which represents current clinical practice in the United Kingdom. Due to the nature of this effectiveness comparator, participants will not be blind to their treatment arm, so will be aware of treatment allocation. We will mitigate for unblinding biases keeping clinician raters, and the senior statistician and health economist blind to allocation.

We will endeavour to have the same researcher to work with the same participant for the duration of the participants' engagement with the trial. In order to ensure unbiased ratings on clinician rated scales, a second research team member will join the study visits for independent clinician ratings. The second researcher will not be present for any discussion regarding treatment or adverse events to reduce the chance of accidental unblinding of the second rater. Participants will be asked explicitly not to disclose their group allocation in the presence of the second independent rater. However, we concede that it is possible for participants to inadvertently disclose their study-arm during study assessments. If a researcher becomes unblinded for an individual participant, a different assessor will replace them for the remaining assessments of this participant.

In addition, data will be collected from each secondary assessor to test the maintenance of blinding. At the three post-intervention assessment time points (week 10, month 4 and month 6) study assessors will be asked by the trial manager

whether they have been
unblinded (at the time of outcome rating) for this participant. The rate (%) of unblinding will be estimated and reported for both the intervention and the control group.

After the 6-month follow-up visit, the need for blinding will not be necessary as we enter the maintenance follow up phase of the trial where all participants can have tDCS if desired. A second research team member will not be required for any clinician rated scales at the 9-month study visit, or during any unscheduled visits during the maintenance follow up phase.

16.8 Baseline data

The baseline assessment takes place within 24 days of the screening assessment (3 weeks +/- 3 days) and on the same day as randomisation (or the day before in case of an evening appointment). The following measures will be collected at baseline: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS, C-SSRS, AD-SUS, EQ-5D-5L, tDCS AEQ, TAQ.

16.9 Trial assessments

Trial assessments are described in section 13.4.2.

16.9.1 Brief description of rating scales

AD-SUS: Adult Service Use Schedule is resource use schedule which can be tailored to capture a broad range of health and social care service use and societal costs, including social care, health care, and productivity losses (Strauss et al., 2023).
Audit-C: Alcohol use disorders identification test consumption (Khadjesari et al., 2017; NICE, 2023) is a brief alcohol screen that reliably identifies patients who are hazardous drinkers or have active alcohol use disorders. It consists of three questions focusing on alcohol consumption frequency and quantity, with a total possible score of 12 over the three items. A score of 5 or more is indicative of heavy alcohol use and with a high risk of alcohol use disorder.
C-SSRS: Columbia Suicide Severity Rating Scale Screen is a rating scale to evaluate suicide risk (Posner et al., 2011).
HAMA: Hamilton Anxiety Rating Scale, consisting of 14 items, which measure psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) (Hamilton, 1959).
HDRS: Hamilton Depression Rating Scale (Hamilton, 1960) is a clinician-administered measure of depressive symptom severity in the previous week, consisting of 17 items on mood, feelings of guilt, suicide ideation, insomnia, agitation or retardation, anxiety, weight loss, and somatic symptoms. This is a commonly used measure to assess change in symptoms in clinical trials which is considered to be acceptable, along with MADRS, by European Agency for the Evaluation of Medicinal Products (EMEA, 2002), that provides a complementary assessment of depressive symptoms (Carmody et al., 2006; Guizzaro et al., 2020). The HDRS scale measures symptom dimensions with limited overlap with MADRS (Fried, 2017), hence providing a robust clinical effect measurement (Fried and Nesse, 2015).

MINI: Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). MINI is a brief structured diagnostic interview, developed jointly by psychiatrists and clinicians for psychiatric disorders (Sheehan et al., 1998).
MADRS: Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979) is 10-item, clinician-rated scale that evaluates depressive symptoms in the past week. Scale is a commonly used measure to assess treatment efficacy, and greater sensitivity to detect treatment-related change has been reported (Mulder et al., 2003). Items are: apparent sadness, reported sadness, feelings of tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel emotions, pessimistic thoughts, and suicidal thoughts. Each item is scored on a 7-point scale. Total score range: 0 to 60. MADRS score >= 18 indicates at least a moderate severity of depressive symptoms, and score and score <= 10 is a measure of clinical remission (Mittman et al., 1997).
MADRS-S: Montgomery-Åsberg Depression Rating Scale-Self report version. MADRS-S is a self-rated version of MADRS consisting of 9 items, with a moderate correlation with MADRS, indicating that this is a complementary measure of depressive symptoms (Svanborg and Åsberg, 1994).
QIDS-SR: Quick Inventory of Depressive Symptomatology Self Report (Rush et al., 2003). Self-rated scale for depressive symptom severity which consists of 16 questions, which provides a complementary measure of depressive symptoms. Total score range: 0 to 27.
AEQ: tDCS Adverse Events Questionnaire. The AEQ questionnaire was developed to capture adverse events during tDCS sessions (Brunoni et al., 2011).
TAQ: Treatment Acceptability Questionnaire (Woodham et al., 2022, 2024). We developed the TAQ to measure participant expectations and acceptability of any intervention, items include treatment outcome, effort needed, ethicality.
YMRS: Young Mania Rating Scale. YMRS is a rating scale to assess hypomanic or manic symptoms, consisting of 11 items, based on participant's report over the previous 48 hours (Young et al., 1978).

16.9.2 Data acquired at each study visit

At initial consultation interview to assess eligibility for study participation (screening):
1) Socio-demographic data: age, gender, ethnicity, marital status, level of education, current occupation, IMD as measured by postcode
2) Clinical data: duration of current treatment, duration of current episode, past psychiatric history, including previous treatments, initial onset of depression, number of previous episodes, hospital admissions, history of self harm and suicide attempts; and past medical history.
3) Clinical diagnosis: MINI
4) Clinical symptom severity: MADRS, YMRS
5) Suicide risk: C-SSRS
6) Adverse events: AEQ
7) AUDIT-C

At week 0, first study visit before randomisation (baseline)
1) Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
2) Suicide risk: C-SSRS
3) Quality of life measure: EQ-5D-5L

4) Service use: AD-SUS in previous 6 months
5) Treatment acceptability: TAQ
6) Adverse events: AEQ

At timepoint 1 (within 5 days of baseline visit)
1) Adverse events: AEQ

At weeks 1, 4 and 7, study visits after timepoint 1(treatment phase visits)
1) Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
2) Suicide risk: C-SSRS
3) Adverse events: AEQ

At week 10, study visit at the end of treatment:
1) Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
2) Suicide risk: C-SSRS
3) Quality of life measure: EQ-5D-5L
4) Service use: AD-SUS
5) Treatment acceptability: TAQ
6) Adverse events: AEQ

At months 4, 6 and 9, study visits for follow up:
1) Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
2) Suicide risk: C-SSRS
3) Service use: AD-SUS (not completed at month 4 or 9)
4) Quality of life measure: EQ-5D-5L (not completed at month 4 or 9)
5) Treatment acceptability: TAQ
6) Adverse events: AEQ

16.10 Follow-up assessments

Follow-up assessments will be acquired at 4 months and 6 months from randomisation. A final follow up will be completed at month 9 after the open-label phase.

Participants who do not respond to repeated attempts at contact will be identified as 'lost to follow-up'. Site staff should perform and document a minimum of three attempts to contact them via phone/email to complete the study visit prior to considering the participant LTFU.

16.11 Late and missed visits

If a participant fails to return for a scheduled study visit within the visit window defined in the study protocol but completes the visit prior to the beginning of the next visit window, that visit is considered to have been completed late. A protocol deviation should be documented on the appropriate protocol deviation log.
If a participant fails to return for a scheduled study visit within the visit window defined in the study protocol and the next scheduled study visit window opens, that visit is considered to have been missed. A protocol deviation should be documented on the appropriate protocol deviation log.

All attempts should be
made to schedule the participant for the study visit as soon as possible so that it is captured late rather than missed completely.

16.12 Unscheduled visits

Participants may be seen for unscheduled visits as needed. During the unscheduled visit, the Investigator will assess the participant's progress and can perform the following assessments: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS, C-SSRS, AEQ.
Review of concomitant medications/treatments.
Record any new or updated adverse events and device deficiencies, if applicable.

16.13 Qualitative assessments

Interviews will be conducted with all consenting participants at baseline. The interview will consist of the Treatment Acceptability Questionnaire (TAQ) questions. All participants in both arms will be asked permission to record their TAQ responses using Microsoft Teams. Baseline qualitative interviews will be analysed using a Codebook Thematic Analysis (Ritchie & Spencer, 1994) to gain understanding about thoughts, feelings and views of tDCS prior to experiencing the treatment.

Interviews will be conducted with approximately 30 participants in each arm at week 10 and month 9 follow up, and 20 clinicians to examine their experiences and views of prescribing tDCS. Interviews will be recorded in MS Teams and transcribed verbatim. From the start of the trial, purposive sampling will be used to explore the diversity of experiences according to gender, age, ethnicity, socioeconomic status and severity of depressive symptoms. Participants will be invited to take part in the interviews until the data are of sufficient depth, breadth, and nuance. We estimate recruiting approximately 30 participants from each arm.

Qualitative data will be analysed using a Codebook Thematic Analysis (Ritchie & Spencer, 1994) to facilitate analysis within and between individual cases and groups of participants. The thematic framework will draw on prior issues around perceived mechanisms of impact, implementation and context, but be responsive to emergent and analytical themes. Once applied to individual transcripts, data will be charted to map and interpret the data set as a whole. Qualitative process data will be analysed prior to the outcome data, but any prospective insights will not be communicated to the wider team until the RCT outcome is known.

Aims of the qualitative process evaluation are to examine: (i) mechanisms of impact, focussing on how tDCS sessions and TAU affect participants' thoughts, feelings and behaviours in the context of their everyday life, immediately after treatment and six months later; (ii) implementation processes, including what supports adherence and delivery in the NHS and reasons for non-adherence and non-completion. We will also explore how individual circumstances (e.g. age, membership of an underserved population, type of TAU) influence treatment experiences.

16.14 Interview recordings

In the assessment interview, we will ask participants for explicit permission to audio-record and/or video-record the session by MS Teams. These recordings will be used

to train and improve
automated speech-to-text and qualitative analysis AI models for assessment for depression. Recordings will be stored on encrypted, access-restricted servers, and any machine-learning workflow will use de-identified audio and/or visual information (all personal identifiers removed before analysis). Participants may decline recording or request that their recording be deleted at any time without affecting their involvement in the study.

16.15 End of the study:

The study will end when on the date of the last participant visit/follow-up visit (month 9) which will conclude the completion of data collection.

16.16 Description of trial procedures by visit

The summary table in section 13.4.2 describes the procedures at each 'visit '(or measurement timepoint) which are also described below. Week -3 (the first screen, up to three weeks before randomisation) through to baseline assessment), randomisation and intervention start at week 0 through to month 9 as the final visit. Once identified through different recruitment sources (e.g., referral by a clinician who obtained consent for contact, direct express of interest in the study by a person), potential participants will be first contacted regarding the study by a researcher who will email them a list of some inclusion/exclusion criteria to assess potential eligibility, this will be followed by a brief telephone screen. Potentially eligible participants will be emailed a copy of the Participant Information Sheet (PIS; via email). The researcher will encourage potential participants to spend as much time as they need asking questions about the study (via email or phone call) and consider whether they wish to participate or not.

As a minimum, study information will be provided to potential participants at least 24 hours prior to initial screening. After reading the PIS and having any questions answered, if the participant is happy to take part in the study, an appointment for screening will be arranged.

Week -3 to 0: Screening session – Usually conducted via video conference, but can take place in person if preferred by the participant. Study information will be discussed Informed Consent to participate in the trial and screening visit will be obtained. If the potential participant is willing, screening will provide an initial determination of eligibility. Specifically, eligibility will be assessed via screening procedures as follows:

- Eligible age range: 18 years old or more.
- Diagnostic interview to confirm a DSM-5 diagnosis of major depressive disorder with current depressive episode: The Mini International Neuropsychiatric Interview, version 7.0 (MINI 7) for DSM-5 (Sheehan et al., 1998) will be administered by trained researchers and reviewed in collaboration with the site's trial psychiatrist to determine a current MDD diagnosis.

- Symptom severity: Montgomery-Åsberg Depression Rating Scale (Montgomery and Åsberg, 1979) will be administered, with moderate severity defined as a score of 18 or more, covering the past 7 days.
- Assessment of suicide risk: Columbia Suicide Severity Rating Scale Screen is a rating scale to evaluate suicide risk (Posner et al., 2011) will be administered, with a response of 'yes' to questions 4, 5 or 6 considered exclusion criteria.
- Assessment of alcohol and substance abuse: Audit-C, Alcohol use disorders identification test consumption (Khadjesari et al., 2017; NICE, 2023) will be administered with a score of 5 or more considered an exclusion.
- Current pharmacological treatments (type, dose, frequency of use, duration of use), current non-pharmacological treatments (type, provider, attendance frequency), past treatments (number of pharmacological, psychological, and other treatments)
- Questions assessing other potential exclusion criteria: comorbid diagnoses (also assessed using MINI), current and previous depression treatments, current physical health conditions, current medications, any cognitive disorder, any implanted devices, any metal in the head, pregnancy, healthcare professional contact details, concurrent enrolment in another interventional study, lack of capacity to consent.

If a participant reports information during the screening assessment that is a clear exclusion for participation, the screening assessment will be paused and discussion with the CI regarding the exclusion will be discussed.

Other information that will be collected at the screening visit include:

- Socio-demographic data: age, gender, ethnicity, marital status, level of education, current occupation, IMD as measured by postcode
- Clinical data: duration of current treatment, duration of current episode, past psychiatric history, including previous treatments, initial onset of depression, number of previous episodes, hospital admissions, history of self harm and suicide attempts; and past medical history.
- Assessment of manic symptoms: measured with Young Mania Rating Scale (Young et al., 1978)
- Adverse events (AEQ)

Pre-baseline administrative procedures – Before the assessment begins, a copy of the consent form alongside a letter of notification is sent to the contact Healthcare Professional (who also receives an information sheet about the study) for that participant. The letter asks the professional to note on the patient's health record confirming that they are participating in this interventional study.

Baseline study visit:

Prior to the randomisation the following measures will be assessed:

- Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
- Suicide risk: C-SSRS

- Service use: AD-SUS in previous 6 months
- Quality of life measure: EQ-5D-5L
- Treatment acceptability: TAQ (Qualitative interview using TAQ if consent given)
- Adverse events: AEQ

Participants will also be asked about general health, medication/psychotherapy treatments or any changes to treatments. If the participant no longer meets inclusion criteria (MADRS score of 18 or above) they will not proceed in the trial.

Subsequently, randomisation will be conducted (as per timing and procedures described in section 16.5). The participant will be notified by telephone of which intervention arm they have been randomised to and a tDCS device will be sent to their home if allocated to the TAU+tDCS arm.

Participants randomised to the TAU arm will have all of the study visits as listed below, but will not engage in the tDCS intervention until after the month 6 visit is completed.

T1, should be scheduled for the earliest time after randomisation (maximum 5 days).

- TAU arm: this visit will consist of a short meeting to record any changes to treatment, AEs and to complete the AEQ.
- TAU+tDCS arm: the participant will have received their tDCS device. During the study visit the research team member will invite the participant to install the dedicated study app. The participants email will be entered into the study app portal, this will send an email to the participant with a link to download the app. Once downloaded the participant will create a password to login to the app. Once logged in, the research team will be able to view the participant in the study app portal where the stimulations can be tracked. The research team member will support the participant to use the tDCS device for their first stimulation session. During the stimulation session the researcher will maintain a discreet presence on the video call or in person without interacting with the participant, unless they are responding to the participant related to the stimulation. After the stimulation session, participants will be administered the AEQ.

The participant will be given the following information/advice about what to do whilst having the stimulation:

- Sit or lie down while using the headset.
- Use the headset on your head as shown.
- Do not use the headset if you have a skin wound.
- Do not apply the headset over areas of skin that lack normal sensations.
- Do not use the headset on other parts of the body.
- Do not apply the headset without the supplied headset pads.
- Do not apply the headset with dried-out headset pads (pads are single use).
- Do not apply the headset outdoors or close to water.
- Do not apply the headset while driving.
- Do not apply the headset during any activity that could lead to a significant risk of injury.
- Do not apply the headset while intoxicated or incapacitated.
- Do not apply the headset in environments with strong magnetic fields.
- The tDCS headset is for you and do not share it with others.

Intervention period - Participants will be directed to use the headset according to the study protocol – 5 times per week for weeks 1 to 3, then three times per week for weeks 4 to 10. The participant will be reminded of the common side effects and asked to contact the study team should they experience any less common side effects or have any concerns or questions about any side effects or the stimulations. They will be reminded of the study mobile number should they experience the need to speak to someone urgently.

Weeks 1, 4 and 7: the following assessments will be completed at the study visit:

- Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
- Suicide risk: C-SSRS
- Adverse events: AEQ
- Participants will also be asked about general health, medication/psychotherapy treatments or any changes to treatments.

Week 10 – post intervention:

All outcome measures listed at baseline are repeated. The post-intervention assessment will take place at the end of week 10 after tDCS sessions for that week have been completed. The following assessments are completed:

- Clinical symptom severity: MADRS, MADRS-S, HDRS, HAMA, QIDS-SR, YMRS
- Suicide risk: C-SSRS
- Quality of life measure: EQ-5D-5L
- Service use: AD-SUS
- Treatment acceptability: TAQ
- Adverse events: AEQ
- Participants will also be asked about general health, medication/psychotherapy treatments or any changes to treatments.
- A proportion of participants will be invited to take part in qualitative interview.

After the week 10 visit participants in the TAU+tDCS treatment arm will be able to continue with 3 maintenance tDCS sessions per week if they would like to. This is optional and is up to the participant to decide. If they choose to continue, they will be reminded that they can stop at any time should they wish to.

Month 4: Follow up – All measures listed above in week 10 are repeated except for AD-SUS and EQ-5D-5L.

Month 6: Follow up – All measures listed above in week 10 are repeated.

Extension follow up phase begins in the maintenance follow up: After the 6 month follow up visit the extension follow up phase of the trial will begin. Participants who had been receiving TAU will be given the opportunity to try the tDCS intervention if they wish. Participants who would like to start tDCS will have a device ordered and an additional study visit arranged to train them how to use the device with a researcher

present for the first tDCS stimulation. The only assessment that will be completed during the tDCS training visit is the AEQ.

Month 9: Follow up – All measures listed above in month 6 are repeated except for AD-SUS and EQ-5D-5L. Follow up qualitative interview will be conducted.

Information and procedures for blinding individuals to randomisation outcome

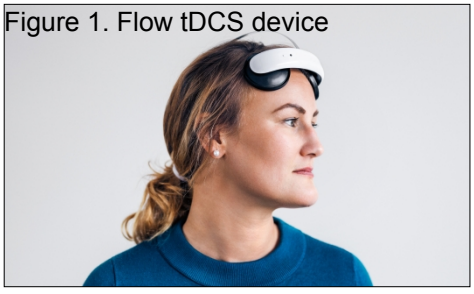
Roles	Blinding	Method of blinding OR justification for unblinding
Trial manager	B	Not told of group assignment, participants asked to conceal this but blinding assessed
Study participants	U	Only unblinded to their own allocation (we are unable to blind participants to receiving tDCS)
Trial therapists	U	Only unblinded to participants who they will see for the duration of the trial, who will be taught to use tDCS devices and asked about any adverse events (required for providing tDCS). Information about other researchers' participants may be mentioned in team meetings but is minimized and discussion of treatment and adverse events that might lead to unblinding will be discussed with PI separately.
Data collectors / Outcome assessors	B	Not told of group assignment, participants asked to conceal this but blinding assessed
Trial Statistician	B/U	Blinded until SAP signed, then unblinded to extract data for DMEC. No interaction with individual participants
Senior Statistician	B	No interaction with individual participants
Principal / Chief Investigators	(U)	Usually blinded, unless participant details need to be conveyed for safety or wellbeing purposes
(independent members of) DMEC	B	No interaction with individual participants
TSC	B	No interaction with individual participants

17 TRIAL TREATMENTS

17.1 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 23cm^2 electrodes built in.

Figure 1. Flow tDCS device



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

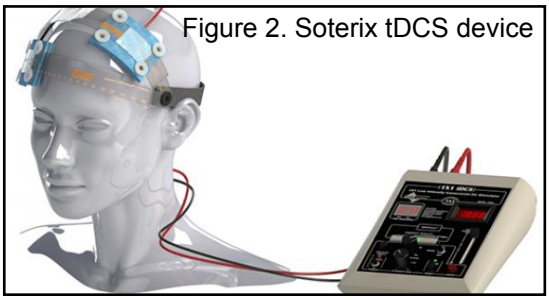


Figure 2. Soterix tDCS device

17.3 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 2).

17.4 Storage and supply of device:

The tDCS headset will be ordered by the research team directly from the manufacturer, Flow Neuroscience. The order will be sent by email and will contain the participant name, delivery address and contact telephone number and/or email address to aid delivery. Participants are made aware that these details will be shared during informed consent they and will be informed again prior to making the order. The device is delivered to the participant's home and is stored at the participant's home. Participants are advised that the tDCS headset is for them and that they should not share it with others (this is included in the PIS).

Participants can keep the tDCS device after the trial.

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

17.6 Dosage schedules:

The device is designed and approved (CE) to be used at home without supervision. 10-week course of active tDCS treatment, consisting of 5 sessions per week for the first 3 weeks followed by 3 sessions per week for 7 weeks, for a total of 36 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 23cm^2. During the first tDCS session, participants will be seated comfortably with their eyes open, and the 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, and that effect sizes continue to increase with longer treatment durations (Nikolin et al. 2023). The tDCS equipment records the duration of each session, and there is an automatic shut-off to prevent unsafe use.

17.7 Dosage modifications: N/A

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

17.9 Concomitant treatments

All participants will continue receiving TAU including all concomitant interventions and service use. We will monitor and record pharmacological and non-pharmacological therapy use, as well as other use of healthcare services throughout the trial, including any changes, at every assessment time-point.

17.10 Trial restrictions

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

17.11 Assessment of compliance with treatment

The tDCS device and associated app 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 the first session, in person or via video link, in order to aid in the initial positioning and to monitor for any adverse events.
The dedicated tDCS device study app will be used to initiate the stimulation, record the number of sessions and limit the number of sessions per day and per week. Via the study app the research team will be able to monitor the number of sessions that are completed by participants and edit the stimulation schedule if necessary.

18 RECORDING AND REPORTING OF ADVERSE EVENTS

18.1 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 • considered significant by the investigator for any other reason 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.

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

18.2 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.

18.3 Recording and reporting of SAEs and SARs

AE data will be collected from participants at every study visit including baseline. AEs captured at the baseline visit will be recorded as medical history. AEs captured after baseline will be recorded in the adverse events log. 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

18.4 Responsibilities

Principal Investigator (PI):

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. 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 and SARs 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.

Trial Steering Committee (TSC): In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC): In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

18.5 Notification of deaths

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

18.6 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.

18.7 Overdose: N/A

18.8 Reporting urgent safety measures

If any urgent safety measures are taken the CI/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.

18.9 Reporting unanticipated AEs to Yellow Card

During the trial, unanticipated, device related adverse events will be reported to Yellow Card Medical devices | Making medicines and medical devices safer.

Unanticipated AEs are defined as AEs that are not anticipated after use of tDCS. These are any AEs that are not listed on the tDCS AEQ.

Only unanticipated AEs that are determined to be device related by the PI will be reported to Yellow Card Medical devices | Making medicines and medical devices safer.

19 STATISTICS AND DATA ANALYSIS

19.1 Sample size calculation

Our previous efficacy RCT in this patient population estimated a 3.6 point reduction in MADRS at the 10-week end of treatment (95% CI 1.1 to 6.1) for active compared with sham tDCS, standardised effect size d = 0.42 (Woodham et al., 2024). tDCS effect size estimates for MDD populations have been d = 0.31 (95% CI 0.15 to 0.47) (Moffa et al., 2020). Parameter estimates from our efficacy RCT (Woodham et al., 2024) inform the sample size calculation: SD active group = 8.81, SD sham group = 8.47; and 15% loss to follow up by 10-week end of treatment, estimating increase to 20% by 6-month assessment.

Based on consideration for the minimum clinically important difference (MCID) to be a reduction of 3 points in our primary outcome scale (MADRS) (Lam et al., 2005; Duru et al., 2008), we calculate that 438 MDD participants (219 per trial arm: TAU and TAU+ DCS) will be required to detect a reduction of 3 points with 90% power using a two-sided t-test at the 5% level and allowing for 20% loss to follow up (Stata command sampsi).

19.2 Planned recruitment rate

During the 6-month internal pilot the planned recruitment rate is 3-4 participants per month at each site. 18-24 participants per month across all sites.
Following the pilot phase the planned recruitment rate is 4-5 participants per month at each site. 24-30 participants per month across all sites.

19.3 Statistical analysis plan

A detailed statistical analysis plan (SAP) will be drafted by the trial statisticians. Briefly, an intention-to-treat approach will be used. Trial arm differences in continuous primary and secondary outcomes at 10-week and 6-month follow up, respectively, will be estimated by linear mixed modelling. Repeated measures of the respective outcome variable will be utilised in the modelling to ensure that in the presence of missing data statistical inferences will remain valid under a less restrictive missing at random assumption. At the minimum outcome measures at 10 weeks and 6 months will be jointly modelled. Such an analysis model will contain the outcome variable (measured at 10 weeks and 6 months) as the dependent variable and trial arm, time, interaction trial arm x time, baseline values of the respective outcome variable and recruitment site as fixed effects. Participant-varying random intercepts will be included to account for the correlation between the repeated measures. For binary secondary outcomes such as treatment response or remission a similar logistic mixed modelling approach will be used.

19.4 Health Economics Analysis Plan

A detailed health economics analysis plan will be drafted guided by the SAP. A cost-utility analysis will estimate the cost effectiveness of the intervention compared to TAU expressed as the cost per QALY at the primary economic end point at the six month follow-up. The primary analysis will take the NHS/PSS perspective on costs

and QALYs will be
estimated using the EQ-5D-5L as per the prevailing NICE guidance. Costs will be collected using an adapted AD-SUS for this population for the six months prior to baseline and at 10 weeks and the 6-month follow-up. EQ-5D-5L utility values will be collected at baseline and 10 weeks and 6-month follow-up and QALYs will be calculated based on linear interpolation assuming a constant rate of change. Generalised linear modelling will be used to adjust costs and QALYs using the baseline covariates specified in the SAP plus relevant baseline economic values (costs, EQ-5D-5L values). Probabilistic bootstrapping of 1,000 pairs of costs and QALYs differences selected with replacement from the sample will promulgate uncertainty around the point estimate of the cost-effectiveness (i.e. the cost per QALY) and plotted onto a cost effectiveness plane. The probability of cost effectiveness for the £20,000 to £30,000 per QALY willingness to pay threshold attributed to NICE will be derived from cost-effectiveness acceptability curves. Sensitivity analysis will explore the impact of missing data, outliers above the 99th percentile and societal costs.

19.5 Economic evaluation:

We will conduct in-depth process evaluation, economic evaluation, and implementation work to investigate operational challenges of integrating home-based tDCS into existing NHS care pathways and to inform scalability in primary care settings.

The following outcomes will be used for the health economics evaluation.

1) Difference in quality-adjusted life-years (QALY) between treatment arms at 10 weeks and 6 months based on EQ-5D-5L.
2) Difference in health and social care costs between treatment arms at 10 weeks and 6 months based on Adult Service Use Schedule (AD-SUS) (Strauss et al., 2023) and clinical records.
3) Incremental cost-effectiveness between TAU and TAU+tDCS treatment arms at 10 weeks and at 6 month follow up measured by cost per QALY.

20 DATA MANAGEMENT

20.1 Data collection tools and source document identification

Individual data will be recorded on the source notes which consist of password protected MS word/PDF documents with records for who completed each study visit and the date. Necessary data will be transferred to the electronic case report form (eCRF).

The CRF design will ensure that adequate collection of data has been performed and that proper audit trails can be kept to demonstrate the validity of the trial (both during and after the trial).

The rating scales are standardised scales, with the exception of the acceptability questionnaire. The CRF will describe the methods used to aid in retention and recruitment, for example telephoning participants to arrange follow up visits.

The institution will keep
records of all participating patients (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.

20.2 Data handling and record keeping

The Chief Investigator will act as custodian for the trial data. Patient data will be anonymised as far as possible (see below for detail). All trial data will be stored in line with the Data Protection Act and archived in line with Sponsor requirements. Source documentation will be recorded in password protected MS Word and/or PDF format and saved on the KCL restricted access SharePoint Trial Management Folder.

The CRF will be a web based electronic data capture (EDC) system that 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.

Source data will be entered by research assistant, senior trial manager, study co-ordinator, PIs and CI, typically within 7 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.

20.2.1 Security

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 date of birth will be entered on the EDC. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC system. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial.

Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance. Data extracts from the randomisation system and MACRO EDC will be requested by the trial statistician as needed for preparing data monitoring reports and data queries. This will be done by submitting an extract request to the KCTU via the ctu@kcl.ac.uk address. Data extracts will be held securely on a KCL server or on OneDrive.

During in-person visits the
informed consent can be printed and signed manually. Manual files will be scanned and uploaded to the ISF and stored in a location at the research site that is secure, in a locked cabinet or drawer.

20.2.2 Data Quality Processes

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst where appropriate for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

The KCTU will provide the study team with Data management plan for Elsevier InferMed MACRO EDC once the system is made live and ready for use.

20.2.3 Database Lock

At the end of the trial, the site PI will review all the data for each participant to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

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.

20.3 Access to Data

Direct access will be granted to the study research team, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections in line with participant consent.

20.4 Archiving

Electronic archiving will be authorised by the Sponsor following submission of the end of trial report. The Sponsor will be responsible for archiving all trial documents. All essential documents will be archived for 25 years after completion of the trial. Any video recordings of study visits or acceptability questionnaires will be transcribed within 1 years of study completion and will then be deleted.
Each research site will be responsible for their own archiving arrangements (as per their Trust/local policies).

21 MONITORING, AUDIT & INSPECTION

Monitoring of this trial will ensure compliance with Good Clinical Practice and scientific integrity will be managed by the study team and overseen from the DMC/TSC. To optimise and maintain quality throughout the trial, TSC monitoring includes ≥ 75% individuals independent from the study team; our procedures also ensure that support and training for undertaking research assessments and handling data. King's Clinical Trials Unit (KCTU) will manage the creation of the eCRF database and randomisation system in collaboration with the CI, statisticians, health economists and study team. The Chief Investigator maintains overall trial responsibilities, working closely with a trial manager to ensure the trial is conducted according to the protocol and KCTU standard operating procedures. A trial

management group (TMG) will include the Chief Investigator, research staff as well as statisticians, health economists and co-investigators as required. The TMG will be responsible for overseeing the day to day functioning of the trial and quality assurance overall. The group will meet every 3 months at a minimum. The Chief Investigator can call for additional TMG meetings if required. The TMG will review recruitment figures, Serious Adverse Events and substantial amendments to the protocol prior to submission to the REC.

22 ETHICAL AND REGULATORY CONSIDERATIONS

22.1 Assessment and management of risk: Distress policy

A member of the research team will be present in person or by video link at the first tDCS session and participants will have observer-rated assessments of their depressive symptoms after 1, 4, 7 and 10 weeks. They will be assessed for depressive symptoms using clinician rated scales, MADRS and HDRS, self report scale MADRS-S, QIDS-SR and suicide risk scale C-SSRS. Any worsening of depressive symptoms or development of suicidal ideation or concerns raised by the participant will be reviewed with the Principal Investigator.

For any urgent concerns of acute self harm or harm to others, the study team member will contact the Principal Investigator, GP, and emergency services. For any concerns that the participant may be at risk of abuse or neglect, the study team member will contact the Principal Investigator and the NHS Trust Safeguarding team. For the South London and Maudsley NHS Foundation Trust: Lambeth: 020 7926 555; Southwark 020 7525 3324 (Appendix 2: Distress Protocol). An addition distress protocol has been developed for the purpose of the qualitative interviews.

22.2 Research Ethics Committee (REC) review & reports

The trial will receive ethical review and approval. Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and relevant documents. Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given and annually until the trial is declared ended.

The Chief Investigator will notify the REC of the end of the trial.If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

22.3 Peer review

The study has undergone an external, independent, expert peer review by the funder.

22.4 Public and Patient Involvement

Patients, service users, and their carers have been involved in the design of the study and will be involved in the interpretation, reporting and dissemination of the findings. We have decided to investigate this topic in collaboration with patients and carers who have had first-hand experience tDCS therapy for depression.

The PPI group will meet twice a year and send representatives to the TMG, TSC and DMEC.

The PPI will lead on advising on what is important to service users (recruitment, ethical and service users' acceptability factors). Input into interview questionnaire and participant-facing materials, write the PPI perspective section for final report, input into the plain language summary, dissemination, and input into implementation development. Required training and support will be identified and provided.

22.5 Regulatory Compliance

The study will not commence until a favourable REC opinion is obtained.
Before any NHS site can be opened to recruit participants, the Chief Investigator/Principal Investigator or designee must receive NHS permission in writing from the Trust Research & Development (R&D). It is the responsibility of the CI/ PI or designee at each site to ensure that all subsequent amendments gain the necessary approvals, including NHS Permission (where required) at the site.

22.6 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

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

22.7 Notification of serious breaches

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

a) the safety or physical or mental integrity of the participants of the trial; or
b) the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during the trial.

22.8 Data protection and patient confidentiality

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

Personal information that is collected will be kept secure and maintained by:
- the creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters
- secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media
- limiting access to the minimum number of individuals necessary for quality control, audit, and analysis

22.9 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator and principal investigators at each site do not report any competing interests that might influence trial design, conduct, or reporting with regards to:
- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

22.10 Indemnity

Indemnity and insurance are provided through KCL/SlaM schemes.

22.11 Amendments

The Chief Investigator will be responsible for the decision to amend the protocol and to decide whether an amendment is substantial. If there is a substantial amendment, the Sponsor will submit a valid notice of amendment to the REC for consideration. The NIHR will prospectively approve any significant protocol amendments. Amendments will be identified in the protocol version.

The Sponsor will also notify the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

22.12 Post trial care

After the trial is completed, the participant will return to their GP and/or psychiatrist and a letter reporting their participation and outcome will be provided to their GP.

22.13 Access to the final trial dataset

The Chief Investigator will have access to the full dataset.

23 FINANCE AND PUBLICATION POLICY

23.1 Funding and support in kind

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	INANCIAL AND NON FINANCIALSUPPORT GIVEN
NIHR	Financial support

23.2 Role of trial sponsor and funder

The trial sponsor, King's College London, assumes overall responsibility for the initiation and management of the trial.

The sponsor and funders have not contributed to the trial design, will not contribute to the data analysis, interpretation and manuscript writing, and may aid in the dissemination of the findings.

23.3 Dissemination policy

On completion of the trial, the data will be analysed and tabulated and a Final Trial Report prepared. The funding boy will be acknowledged within the publications. Participants will be notified of the outcome of the trial by a specifically designed newsletter. If a participant specifically requests results, this information will be provided after the Final Trial Report has been compiled.

23.4 Authorship eligibility guidelines and any intended use of professional writers

Authors who have made substantial contributions to the design, study process, data analysis and interpretation, and/or to the manuscript will be granted authorship on the Final Trial Report.

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25 APPENDICIES

25.1 Appendix 1 - Risk

Risks associated with trial interventions
☐ A ≡ Comparable to the risk of standard medical care
☒ B ≡ Somewhat higher than the risk of standard medical care
☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):
Meta-analysis show that participants with depression who receive the active tDCS treatment are not able to distinguish the adverse effects from a sham placebo tDCS treatment and there is no difference in the discontinuation rates (Mutz et al., 2018; Brunoni et al., 2016; Meron et al., 2015).

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?
Intervention	Body system/Hazard	Activity
tDCS	redness, tingling , itching, burning sensation, headache, discomfort	Usual duration of each session is 30 minutes and there is an automatic shut off to prevent additional use. No serious adverse effects have been observed at the 2 mA tDC that will be used in the present study.

Outline any other processes that have been put in place to mitigate risks to participant safety:
The research fellow will be present in person or by video link for the first tDCS session. We are able to monitor use in real-time and we can follow up right away for any concerns. We have regular follow up visits by video conference in which we assess progress and can follow up on any concerns. We have a dedicated 24-hour mobile phone which all participants can contact at any time for any concerns.

Outline any processes that have been simplified based on the risk adapted approach:
We will use the tDCS AEQ to assess for any adverse events after the first tDCS session and at weeks 1, 4, 7 and 10 and at months 4, 6 and 9.

25.2 Appendix 2 - Distress Protocol

Participant ID: Visit number:
Date:

Has the visit been curtailed because the participant became distressed? Yes No
If yes: 1) Invite the participant to talk about how they are feeling, either to the study team member or ring the Principal Investigator. 2) Notify the Principal Investigator. 3) Please provide an outline of what happened and the outcome (continue on back as needed):
Is the participant's MADRS score higher than at baseline? Yes No Has the participant's MADRS score been increasing over the past couple of weeks? Yes No Has the participant raised any concerns about their mood? Yes No
If yes to any of the above: 1) Invite the participant to talk about how they are feeling, either to the study team member or ring the Principal Investigator. Give the participant a copy of the Participant Information Sheet, pointing out the Principal Investigator's contact information. 2) Notify the Principal Investigator. 3) Please provide an outline of what happened and the outcome(continue on back as needed):
Is the participant at risk of abuse or neglect? Yes No
If yes: 1) Notify the Principal Investigator. 2) Contact the NHS Trust Safeguarding team. 3) Please summarise your concerns (continue on back as needed):