Spaced Transcranial Direct Current Stimulation for Treatment-Resistant Depression: A Home-Based Feasibility and Safety Study
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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title

Spaced Transcranial Direct Current Stimulation for Treatment-Resistant Depression: A Home-Based Feasibility and Safety Study

Study Summary

Background

Major Depressive Disorder (MDD) is a leading cause of disability worldwide, exhibiting a lifetime prevalence of up to 21%.[1] Despite the effectiveness of first-line treatments, such as antidepressant medication and psychotherapy, up to 55% of MDD patients will develop treatment-resistant depression (TRD).[2] These findings underscore the critical need for innovative therapeutic strategies in MDD management.

In the context of TRD, the limitations of existing therapeutic options are notable. Electroconvulsive therapy (ECT), while effective for severe cases, is often marred by concerns regarding cognitive side effects and the requirement for anesthesia.[3] Transcranial magnetic stimulation (TMS), though non-invasive, is limited by its high costs.[4] These interventions also require frequent in-clinic visit, imposing significant logistical and financial burdens on patients, particularly those in underserved or rural areas. In that context, transcranial direct current stimulation (tDCS) has emerged as a promising alternative.

tDCS offers several key advantages over other neuromodulation intervention, making it a more accessible and versatile option for clinical applications. tDCS is significantly less expensive, as it does not require complex equipment, specialized infrastructure, or highly trained staff, thereby reducing costs substantially.[5] tDCS also has a high safety profile characterized by minimal to no side effects.[6] Additionally, tDCS is simpler to administer and patients can be trained to self-administer treatment, enabling convenient home-based care.[7–11] These advantages position tDCS as a practical and promising alternative neuromodulation intervention for TRD.

Although tDCS is not yet FDA-approved for MDD, growing evidence supports its therapeutic effects.[12,13] However, subsequent work in TRD specifically yielded mixed results.[14,15] To enhance the neuroplastic effects of tDCS, preclinical evidence highlights the advantages of 'spaced' protocols**.** Our team recently conducted the first open-label study of an intensive spaced tDCS protocol in 30 participants with TRD.[16] The protocol demonstrated strong feasibility, safety, and preliminary evidence of therapeutic effects. This remains to be confirmed in a randomized controlled trial (RCT).

Objective

We previously conducted an open-label study of spaced tDCS for TRD in a clinical setting, which yielded preliminary evidence of feasibility, safety, tolerability, and potential therapeutic effects. To build on these findings, we initiated a clinic-based RCT. However, recruitment has been severely limited due to the logistical demands of daily clinic visits, and this study will be terminated. These recruitment challenges underscore a key limitation of clinic-based neuromodulation and support the need to evaluate a home-based protocol. The current study is therefore designed to assess the feasibility, safety, and tolerability of home-based spaced tDCS, with the goal of informing a future randomized trial using a remotely supervised delivery model.

Aims and Hypothesis

Aim: To evaluate the preliminary feasibility, safety, and tolerability of home-based spaced tDCS in an open-label study of participants with TRD.

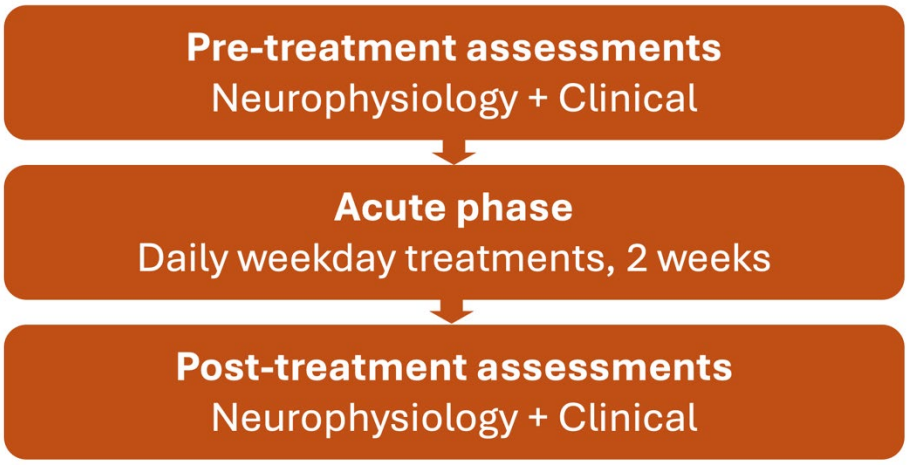
Hypothesis: Home-based spaced tDCS will be feasible (as defined by recruitment, retention, and adherence), safe (as defined by the incidence of serious adverse events), and tolerable (as defined by the incidence of adverse events). Findings from this pilot study will inform the design of a subsequent randomized controlled trial.

Methodology Overview
This will be a pilot, prospective, single-arm, open-label feasibility study of home-based spaced tDCS. Treatment will be delivered over a 2-week period with daily weekday treatments. Participants will self-administer treatment at home under direct remote supervision.

Study Population
10 participants, aged 18-85, diagnosed with MDD according to DSM-5 criteria and exhibiting at least moderate treatment-resistance.

Study duration
1 year

1.2 SCHEMA


Pre-treatment assessments
Neurophysiology + Clinical
Acute phase
Daily weekday treatments, 2 weeks
Post-treatment assessments
Neurophysiology + Clinical

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening	Baseline assessment	Treatment Phase - 2 weeks	1-week post-treatment reassessment	2-week post-treatment reassessment	3-week post-treatment reassessment	4-week post-treatment reassessment	8-week post-treatment reassessment	12-week post-treatment reassessment
Informed consent form and ACE	X								
Demographics	X								
Medical history	X								
Pregnancy Test	X$^{\Omega}$	X$^{\Omega}$							
ATHF – current and lifetime	X								
MINI	X								
TASS	X								
MSSI	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
MADRS *	X	X	X	X	X	X	X	X	X
QIDS-SR *	X	X	X	X	X	X	X	X	X
PHQ-9*	X	X	X	X	X	X	X	X	X
Neurophysiology (TMS-EEG, TMS-EMG, rsEEG)		X		X			X		
tDCS	X$^{\Omega}$	X$^{\Omega}$	X						

*These questionnaires will be completed after treatment sessions 5 and 10 during the Treatment Phase

$^{\Omega}$ This can be done during visit 1 or 2. If the screening visit is remote, at visit 2, a pregnancy test will be confirmed negative prior to the tDCS test procedure.

2 INTRODUCTION

1.2 STUDY RATIONALE

Major depressive disorder (MDD) is a highly prevalent condition with substantial interpersonal and socioeconomic impact. While first-line treatments are effective for many, a significant proportion of patients remain symptomatic and develop treatment-resistant depression (TRD). Transcranial direct current stimulation (tDCS) has emerged as a scalable, low-cost alternative with potential for home-based treatment. However, its efficacy in TRD remains uncertain. We previously demonstrated the feasibility, safety, tolerability, and preliminary therapeutic effects of spaced tDCS in a clinical setting.[16] To fully assess its scalability, further investigation in a home-based setting is necessary.

1.3 BACKGROUND

MDD is a prevalent public health issue in the United States, affecting approximately 21 million individuals annually and contributing to an economic burden of $326 billion.[17,18] A reanalysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial reported a cumulative remission rate of just 35% after four treatment courses, substantially lower than the originally reported 67%.[19] Up to 55% of patients continue to experience symptoms despite multiple treatments, progressing to TRD.[2]

Depression is increasingly conceptualized under the neuroplasticity deficit hypothesis, which posits that an imbalance in excitatory and inhibitory neural activity impairs adaptive neural processes.[20–22] Neuroplasticity—the brain's capacity to adapt through structural and functional changes—is central to both the pathophysiology and treatment of depression. A critical component, synaptic plasticity, involves the modulation of synaptic connections via mechanisms such as long-term potentiation (LTP).[22,23] In depression, maladaptive plasticity manifests as reduced synaptic reorganization and diminished structural changes, including impaired dendritic spinogenesis and synaptogenesis, both essential for neural network remodeling. Imaging and postmortem studies have shown significant reductions in grey matter volume in regions like the hippocampus and prefrontal cortex, correlating with decreased neuronal and glial density.[24] Stress-related mechanisms, including microglial activation and elevated cortisol levels, further exacerbate these deficits, limiting the brain's capacity for adaptive plasticity.[24] Importantly, neuroplasticity deficits have been shown to be more severe in TRD than in MDD, underscoring the need to address these impairments with novel interventions.[25]

This hypothesis underpins interventional approaches for TRD that aim to enhance neuroplasticity. Electroconvulsive therapy (ECT), the gold standard for TRD, increases glutamate and GABA activity, elevates brain-derived neurotrophic factor (BDNF) levels, reduces excitotoxicity, promotes dendritic sprouting and synaptogenesis, and normalizes dysregulated neural connectivity patterns, resulting in increased hippocampal volume.[26,27] Similarly, ketamine, a rapid-acting antidepressant increasingly used in TRD, induces a glutamate surge that activates AMPA receptors, stimulates dendritic spine growth and synaptogenesis, and engages the mTOR pathway, alongside increasing BDNF release and modulating GABA levels in depression-related brain regions.[27,28] Lastly, repetitive transcranial magnetic stimulation (rTMS), a first-line treatment for TRD, enhances neuroplasticity by modulating glutamate and GABA activity, promoting synaptic plasticity through LTP, increases BDNF levels, and improves structural and functional brain connectivity.[27,29]

Despite the effectiveness of these interventional approaches, scalability remains a significant challenge. ECT is cost- and labor-intensive, requiring anesthesia and often leading to cognitive side effects, which contribute to low patient acceptability.[3,30] Ketamine is increasingly used for TRD, but the need for in-clinic delivery, along with concerns about cardiovascular and cognitive side effects, long-term safety, and abuse potential, limits its broader adoption.[31] rTMS, with its favorable side effect profile, is recommended as a first-line treatment for TRD; however, its accessibility is constrained by high costs, the need for certified operators, and in-clinic administration.[4,27] These barriers, combined with insurance coverage gaps, create significant obstacles for patients, particularly those in remote areas or with demanding schedules.[4]

In this context, transcranial direct current stimulation (tDCS) has emerged as a promising alternative that also targets neuroplasticity. tDCS is a non-invasive neuromodulation technique that uses low-intensity electrical currents to modulate cortical excitability. Its putative mechanism of action involves altering neuronal membrane potentials, thereby influencing cortical excitability.[32] tDCS delivers a constant direct current through electrodes placed on the scalp, enabling targeted modulation of specific brain regions. In depression, tDCS is applied to the dorsolateral prefrontal cortex (DLPFC) to target prefrontal-limbic circuits implicated in mood regulation.[33] Depending on the polarity, tDCS can either depolarize neurons with anodal stimulation, or hyperpolarize the cathodal stimulation.[34] These changes in excitability are thought to facilitate long-term neuroplasticity changes.[35,36] Anodal tDCS, which enhances cortical excitability by depolarizing neuronal membranes, creates conditions favorable for LTP, a process critical for synaptic strengthening and adaptive neural network remodeling.[32] This induction of LTP is mediated by increased calcium influx and activation of N-methyl-D-aspartic acid (NMDA) receptors, which are essential for synaptic efficacy and plasticity.[36] By restoring the balance between excitatory and inhibitory signaling, anodal tDCS directly targets the disrupted neural dynamics seen in depression.[37] Moreover, tDCS has been shown to increase brain-derived neurotrophic factor (BDNF) levels, which supports synaptic growth and dendritic branching, further facilitating the reorganization of maladaptive circuits.[38] These mechanisms extend beyond the stimulation site, as tDCS-induced excitability changes in the DLPFC influence interconnected networks, such as the limbic system, improving mood regulation and cognitive functions.[39] Taken together, these effects suggest that tDCS promotes corrective neuroplasticity as a central mechanism to counteract depression's pathological changes.

tDCS offers several key advantages over other neuromodulation intervention, making it a more accessible and versatile option for clinical applications. tDCS is significantly less expensive, as it does not require complex equipment, specialized infrastructure, or highly trained staff, thereby reducing costs substantially.[5] tDCS also has a high safety profile characterized by minimal to no side effects.[6] Additionally, tDCS is simpler to administer, requiring no precise coil positioning, and patients can be trained to self-administer treatment, enabling convenient home-based care.[7–11] These advantages position tDCS as a practical and promising alternative neuromodulation intervention for TRD. Although tDCS is not yet FDA-approved for depression, growing evidence supports its therapeutic effects.[12,13] A landmark randomized controlled trial (RCT) of 120 MDD participants found that active tDCS was superior to placebo (mean difference: 5.9 points; p=0.03; d=0.43) and had comparable efficacy to sertraline (p=0.35).[40] A subsequent RCT involving 245 MDD participants also found that tDCS was superior to placebo (mean difference: 3.2 points; p=0.01; d=0.43).[41] So far, meta-analyses suggest that active tDCS significantly outperforms sham tDCS in reducing depressive symptoms, with effect sizes ranging from 0.31 to 0.46 for continuous depression scores, response rates of 30.9% versus 18.9%, and remission rates of 19.9% versus 11.7%, corresponding to a number needed to treat (NNT) of 6–9 for response and remission.[12,13,42,43] However, subsequent work in TRD specifically yielded mixed results. The DepressionDC trial, a triple-blind, multicenter RCT, evaluated tDCS as an adjunct to SSRI treatment in TRD and found no significant difference in depression symptom reduction between active and sham tDCS after six weeks, with both groups showing comparable

response and remission rates.[15] The PsychotherapyPlus trial, a double-blind, multicenter RCT, evaluated tDCS augmentation of cognitive behavioral therapy (CBT) for TRD and found that while all patients improved significantly regardless of group, there was no added benefit of active tDCS over sham-tDCS or CBT alone.[14] These negative results may stem from sub-optimal stimulation parameters. Conventional tDCS is typically delivered once daily for 30 minutes.[40,44] This approach was primarily selected based on historical precedent and derived from experiments conducted in healthy adults.[37] Therefore, these parameters are most likely to be insufficient to treat TRD. Indeed, evidence indicates that neuroplasticity deficits are more pronounced in TRD compared to MDD, with TRD patients showing greater neurophysiological impairments.[25] **To enhance the neuroplastic effects of tDCS, preclinical evidence highlights the advantages of 'spaced' protocols.** Spaced tDCS involves delivering two or more tDCS sessions separated by intervals of several minutes.[23,45] While conventional single-session anodal tDCS primarily activates early LTP neuroplasticity mechanisms, with effects lasting up to 3 hours, spaced tDCS engages late LTP mechanisms, which induce more enduring effects and involves more complex cellular and molecular processes, including new protein synthesis, leading to enhanced synaptic efficacy that can persist for days.[46–48] Engagement of late LTP neuroplasticity mechanisms has recently been demonstrated in the human motor cortex using spaced stimulation, where 20-minutes intervals were found to be more effective than contiguous sessions (no interval) or long intervals (3 hours).[23,45] There is ongoing debate regarding the optimal spacing interval between sessions.[49] Some studies suggest a minimum of 50 minutes for maximal effects; however, these findings originate from rat hippocampal slice studies on cellular plasticity, not human or clinical research.[49–54] Moreover, these preclinical studies primarily examined the effects of two stimulation trains rather than the cumulative impact of multiple sessions. Using intermittent theta burst stimulation (iTBS), a type of TMS protocol, no increase in cortical excitability was observed between the first and second sessions, but a marked increase was seen with the third session—greater than that of the first—when applied at 15-minute intervals.[55] This demonstrates that iTBS neuroplasticity effects can be accretive under such conditions. These findings are more relevant to understanding the neurophysiology of spacing paradigms on cortical activity than extrapolating from isolated animal brain samples. This approach has not been tested with tDCS, but current evidence similarly suggests that shorter intervals are optimal.[23,45]

Our team recently conducted the first open-label study of a spaced tDCS protocol in 30 participants with TRD.[16] The protocol demonstrated preliminary evidence of feasibility, with a retention rate of 93.3% and an adherence rate of 99.7%, and was well-tolerated with no serious adverse events reported. 17-item Hamilton Depression Rating Scale (HAMD) scores improved significantly, decreasing from a mean of 21.3 (SD = 3.0) at baseline to 15.3 (SD = 6.3) at 1 week, and 13.2 (SD = 7.1) at 4 weeks. A repeated measures ANOVA revealed a significant effect of time on HAMD scores ($F(2, 52) = 29.131$, $p < .001$, $\eta p^2 = .528$). At 4 weeks post-treatment, the response rate was 46.4%, and the remission rate was 32.1%, comparable to outcomes observed with rTMS.[56]

Lastly, a major limitation of current interventions for TRD is the need for frequent in-clinic visits, which impose significant logistical and financial burdens on patients, particularly those in underserved or rural areas.[4] tDCS, because of its simplicity and ease of use, can be self-operated by patients, which opens the door for home use. Recent data suggest that home tDCS can be delivered safely under remote supervision for depression.[8,57] Findings from a recent 10-week, fully remote, double-blind, RCT demonstrated significant improvements in depressive symptoms, clinical response, and remission rates for active tDCS compared to sham.[7] This study also reported high acceptability and safety, emphasizing the potential of home-based tDCS to provide a scalable and effective treatment for MDD while overcoming barriers associated with traditional in-clinic interventions.

In addition to advancing the efficacy of tDCS, there is a crucial need to deepen our understanding of its neurophysiological mechanisms and to develop reliable biomarkers

for its application. *The combination of transcranial magnetic stimulation with electroencephalography (TMS-EEG) and electromyography (TMS-EMG), alongside resting-state electroencephalography (rsEEG), are powerful neurophysiological techniques for these purposes. By targeting specific brain regions with TMS and concurrently recording the resultant electrical activity via EEG and EMG, it is possible to directly perturb neural circuits and observe immediate changes in brain function, shedding light on the neural underpinnings of psychiatric disorders*.[58] Distinct from subjective self-report measures or behavioral tasks, these neurophysiological methods offer a direct and objective assessment of neural activity and facilitate a more accurate evaluation of brain function and connectivity patterns. Numerous studies have demonstrated the utility of these techniques in elucidating neurotransmitter regulatory mechanisms, biological target engagement, and biomarker discovery.[58–70] TMS-EEG can be used to assess TMS-evoked potentials (TEPs) over the dorsolateral prefrontal cortex (DLPFC), providing insights into cortical reactivity and connectivity. TMS-EMG can be used to measure motor-evoked potentials (MEPs) and paired-pulse paradigms such as short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), long-interval intracortical inhibition (LICI), and cortical silent period (CSP), which reflect inhibitory and excitatory balance. Additionally, rsEEG can be used to capture spectral power and functional connectivity at rest, both of which have been linked to MDD pathophysiology and treatment response.[71–77] Collectively, these tools provide objective, circuit-level indices of neuroplasticity and cortical function. In this study, they will be used to explore mechanistic effects of spaced tDCS and to identify candidate biomarkers associated with clinical response.
Our primary objective is to evaluate the preliminary feasibility, safety and tolerability of spaced tDCS for TRD through a home-based open-label study using remote supervision. Additionally, we aim to investigate neurophysiological tools for mechanistic insights into spaced tDCS and biomarker discovery. Positive findings will support a subsequent NIH grant application for a RCT.

1.4 RISK/BENEFIT ASSESSMENT

1.4.1 KNOWN POTENTIAL RISKS

Known Potential Risks

tDCS has been extensively studied over the past 25 years, with substantial evidence supporting its safety and tolerability.[6,78,79] A review of over 33,200 tDCS sessions, including 4,160 in patients with depression, found no serious adverse events (SAEs), including no worsening of mood disorders.[6] The most common side effects were mild and transient, such as itching (39.3% in active treatment vs. 32.9% in placebo), tingling (22.2% vs. 18.3%), headache (14.8% vs. 16.2%), burning sensation (8.7% vs. 10.0%), and discomfort (10.4% vs. 13.4%).[80] Cases of mild, self-resolving erythema or skin rash have been reported, resolving shortly after treatment.[16,81,82] Skin burns under electrodes are extremely rare and are thought to result from equipment malfunction, with no reports of long-term dermatological complications.[9,83–94] Manic or hypomanic switches in bipolar patients have been infrequently documented (11 cases), but a direct causal link to tDCS remains unclear.[87,95–97] Importantly, tDCS has not been associated with cerebral edema, blood-brain barrier changes, or significant thermal skin damage. Long-term safety data show no cumulative adverse effects, and there have been no reports of tDCS-induced seizures.

Home-based tDCS has demonstrated a favorable safety profile across multiple studies, with no reports of SAEs. A large-scale analysis of 6,779 remotely supervised sessions confirmed high tolerability, with mild and transient side effects similar to in-clinic studies.[11] A recent fully remote,

multisite randomized controlled trial also confirmed high acceptability and safety over a 10-week treatment period.[7]

Safety Considerations and Risk Mitigation

Ensuring participant safety is a central priority, particularly given the at-home, self-administered nature of this intervention. To minimize risks, rigorous safety measures have been implemented. All participants will remain under the care of their primary providers, with tDCS serving as an adjunct rather than a replacement for standard treatment. At the initial consultation, participants will be educated on alternative treatment pathways and trained in the proper use of the tDCS device. The first treatment session will take place in the clinic under direct supervision, allowing for hands-on instruction, verification of correct setup, and assessment of individual tolerability.

Subsequent sessions will be conducted at home under real-time, remote supervision via a secure, HIPAA-compliant telehealth platform that ensures direct one-on-one communication between participants and trained clinical research coordinators (CRCs), while preventing interaction between participants. To prevent unauthorized use, the device requires a study staff-provided activation code before each session, and all session data—including compliance, impedance levels, and usage patterns—will be automatically logged. Participants must remain in front of their computer for the full duration of the treatment session, just as they would be required to stay in the treatment room during in-clinic administration. While brief movements such as stretching or bathroom breaks are permitted, extended periods off-camera will not be allowed. Participants may engage in non-disruptive activities such as reading, watching videos, or working on their computer, but must not cook, clean, drive, or engage in any activity that could interfere with treatment. Failure to adhere to these requirements will result in removal from the study to ensure both safety and scientific validity.

To mitigate dermatological risks, daily remote skin inspections will be conducted before and after each session. Participants will be instructed to avoid creams, makeup, or irritants before treatment and to cleanse the skin gently with mild soap. Any mild skin irritation will be monitored, and adjustments such as extending the acute phase over four weeks or modifying electrode placement will be made if needed.

Psychiatric risks, including symptom worsening or suicidality, will be closely monitored through structured mood assessments. Should psychiatric symptoms deteriorate, crisis intervention protocols will be in place, including immediate referral to the participant's primary provider or emergency services if indicated.

Equipment Care and Compliance

Participants will sign an equipment care agreement acknowledging responsibility for the study-provided tDCS device and accessories. This agreement ensures participants understand the need to handle the equipment properly, prevent unauthorized use, and return the device upon study completion or early termination.

Neurophysiology Assessment

The EEG cap contains gel on the inside, which may feel sticky and may cause mild skin irritation or allergic reactions to adhesives and slight discomfort from placing and removing soft foam pads during the sessions. Participants have the option to wash and dry their hair at the end of the session, and these substances can be easily cleaned during this process.

There are no known long-term adverse effects reported with the use of TMS, but the most common side effect is a mild headache experienced by approximately 25% of subjects. Pain, in general, is relatively rare, with rates typically between 2% and 10% across reviewed studies. If pain is reported, stimulation is paused or adjusted, and the participant may be withdrawn if discomfort persists, ensuring the procedure does not cause ongoing or intolerable pain.

According to the FDA, a significant risk device is an investigational device designed to be implanted or otherwise presents a serious risk to the health, safety, or welfare of a subject. Our designation of non-significant risk status is based on the following summary:

1. There is no implant related to TMS.
2. Subjects can drive home or return to work immediately after a TMS session, with no specific contraindications.
3. The most common side effect of TMS is a mild headache or scalp pain.

Additional considerations include:

- Certain Medical Diagnoses: Subjects with epilepsy or stroke may be at increased risk for a seizure due to brain activation by TMS. Therefore, individuals with a history of epilepsy will be excluded from the study. For a typically healthy person, a TMS-induced seizure is very unlikely (i.e., <1/10,000 treatments).
- Noise: The TMS device produces a clicking sound. To minimize this, participants will be given protective earplugs or headphones.
- Hearing Loss: This is preventable with the use of foam earplugs or headphones.
- Nausea: Although uncommon, approximately 5% of subjects may experience nausea during the experiment. Subjects can discontinue the experiment if they experience any discomfort.
- Pain: Patients may experience temporary pain from muscle activation by TMS.

Clinical assessments and self-report questionnaires
Patients might experience emotional discomfort during clinical assessments or when disclosing personal information in questionnaires. Participation is voluntary, with the option to decline answering any questions or withdrawing from the study at any point.

Worsening of Depression Symptoms
By virtue of the population, there is a risk of worsening depression symptoms. While participating in this study, if symptoms worsen to the point where they need psychological or medical support, patients will be given resources for emergency and support services, including an assessment from an on-site physician. If a patient's symptoms require urgent attention, they will be provided with emergency and support contact information relevant to that site. Participants will be informed to call 911 and present to the nearest emergency room or contact: the University of California San Diego at (619) 543-6400. UCSD hotlines are staffed 24 hours a day, 7 days per week. For similar hotlines outside of the San Diego area, they can consult www.suicide.org. We have developed multiple steps to ensure patient safety throughout this trial. Participants will be educated beforehand about alternative treatment pathways available to them, including hospitalization, as well as alternative interventional treatments outside the context of a study, such as TMS, ECT or ketamine. Participants who develop acute suicidal risk requiring admission to the hospital will be removed from the study.

Risk to confidentiality
There is a rare risk that confidentiality could be breached in this study. It is possible, but extremely unlikely, that breaches in confidentiality could impact future insurability and/or employability.

1.4.2 KNOWN POTENTIAL BENEFITS

Participants may experience symptom relief and improved mood regulation, as tDCS has demonstrated antidepressant effects in prior clinical trials. The home-based design reduces logistical and financial burdens, allowing participants to receive treatment in a familiar setting while maintaining daily activities. Additionally, participants will receive comprehensive psychiatric monitoring, including regular mood assessments and real-time supervision, ensuring early detection of symptom changes and timely intervention. By participating, individuals contribute to advancing depression research and potentially shaping future, more effective, and widely accessible treatments for TRD.

1.4.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

tDCS is associated with mild and transient dermatological side effects, primarily skin irritation or erythema, which will be closely monitored. Psychiatric safety measures, including structured mood assessments and crisis intervention protocols, will be in place to address any symptom worsening, and individuals at imminent suicide risk will be excluded from the study. All participants will receive a 24-hour suicide crisis hotline and will be instructed during the consent process to seek immediate support if they feel unsafe. Throughout the study, participants will have direct access to the clinic for support and crisis intervention. While there is no clear evidence that tDCS worsens depressive symptoms, any depression treatment carries a theoretical risk of increased suicidality if motivation improves before mood symptoms fully resolve. Given that symptom severity can fluctuate due to external factors, worsening symptoms during the study would not necessarily indicate a treatment-related effect. Adverse reactions will be assessed daily during tDCS sessions, ensuring real-time symptom monitoring by study staff. Any safety concerns, including participant-reported worsening symptoms, will be promptly escalated to the PI and appropriate personnel for timely intervention. A clinician will be available during treatment hours, and participants will have the option to discuss any concerns or symptom changes remotely. Overall, the potential benefits—including symptom improvement, reduced treatment burden, and increased access to neuromodulation—outweigh the minimal risks. Additionally, this study will contribute valuable clinical and neurophysiological data, advancing the understanding of spaced tDCS for TRD and informing future large-scale clinical applications.

2 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the feasibility, safety and tolerability of a spaced tDCS for TRD in a home-based setting	Feasibility: recruitment and retention rates, as well as protocol adherence. Safety: number of serious adverse events (SAEs). Tolerability: number of adverse events (SEs).	Gather feasibility, safety and tolerability data to inform a subsequent larger RCT.
Secondary		
To evaluate the therapeutic effects of a spaced tDCS protocol in reducing depressive symptoms for TRD.	Score changes on the validated clinician-rated Montgomery–Åsberg Depression Rating Scale (MADRS) pre- to post-treatment.	Gather preliminary effectiveness data for power calculation considerations in a subsequent RCT.
Exploratory		
To explore neurophysiological changes induced by spaced tDCS using TMS-EEG, TMS-EMG, and rsEEG, and to identify candidate biomarkers of treatment response	Changes in TEPs (DLPFC), MEPs and paired-pulse TMS-EMG metrics (e.g., SICI, ICF, LICI, CSP), and rsEEG spectral power and connectivity.	Gather data regarding mechanism of action of treatment and biological marker of treatment response.

3 STUDY DESIGN

3.1 OVERALL DESIGN

Overall approach
This will be a pilot, prospective, single-arm, open-label feasibility study of home-based spaced tDCS. Treatment will be delivered over a 2-week period with daily weekday treatments. Participants will self-administer treatment at home under direct remote supervision. Pre- and post- treatment neurophysiological biomarkers sessions will also be carried out.

Participants
12 participants aged 18-85 with MDD, confirmed using the Mini-International Neuropsychiatric Interview (MINI), will be recruited using consecutive sampling with the goal of obtaining usable data from 10 given the anticipated 20% drop out rate. Eligibility will require meeting criteria for TRD of at least moderate severity, defined as failure to respond to at least one antidepressant medication trial rated at level 3 on the Antidepressant Treatment History Form: Short Form (ATHF-SF). Participants must also score at least 20 on the MADRS and maintain a stable medication regimen for at least 4 weeks prior to starting tDCS treatment.

Recruitment
Participants will be recruited through self-referrals, treating physician referrals, and the UC San Diego Health Interventional Psychiatry Program. Preliminary screening will be conducted via chart review under a partial waiver of HIPAA Authorization, followed by physician evaluation. Eligible candidates will be contacted by the study team via telephone for further screening, and those interested will attend an in-person screening visit.

Recruitment efforts will include IRB-approved flyers at UCSD campuses, social media advertisements (Instagram, Twitter, Facebook), ClinicalTrials.gov listings, and outreach within the Interventional Psychiatry clinical program. This program primarily serves UC San Diego Health patients but also consults individuals outside the catchment area, ensuring a diverse and representative TRD sample.

All study visits will take place at UC San Diego Health Interventional Psychiatry Program locations, including Dove Canyon Clinic (16918 Dove Canyon Rd), La Jolla Outpatient Clinic (8950 Villa La Jolla Dr, Suite C101), and East Campus Medical Center (6655 Alvarado Rd). Participants will have the option to complete the screening visit and 8- and 12- week post treatment visits via UCSD Zoom telehealth technology. Participants will undergo comprehensive diagnostic assessments to confirm TRD eligibility and provide informed consent before further screening. Adverse and serious adverse events will be monitored and recorded at all visits to ensure participant safety.

Inclusion criteria: Eligible participants will be adults aged 18-85 years with a diagnosis of a major depressive episode confirmed on the MINI and a MADRS score ≥ 20, who pass the TMS Adult Safety Screening (TASS). They will need to have either failed to achieve clinical response to an adequate antidepressant trial (ATHF-SF score ≥ 3) or shown intolerance to at least two inadequate trials (score 1 or 2), without psychiatric illness due to a general medical condition. Participants will be voluntary outpatients at the UCSD Health Interventional Psychiatry Program, capable of providing informed consent and willing and able to comply with all study procedures. Additionally, participants will need to have a stable internet connection and a device compatible with Microsoft Teams or UCSD telehealth Zoom to facilitate remote communication and engagement in study activities.

Exclusion criteria: Exclusion criteria include a diagnosis of bipolar disorder, schizophrenia-spectrum disorders, or current psychotic symptoms, as well as primary obsessive-compulsive disorder, post-traumatic stress disorder, anxiety disorder, dysthymia, or personality disorder assessed to cause greater impairment than MDD. Individuals with moderate or severe substance use disorder within the past 3 months, clinically significant suicidality, or chronic depression lasting over 5 years are excluded. Additional exclusions are current pregnancy or lactation, lack of adequate birth control in women of childbearing age, unstable medical illnesses, neurological disorders, contraindications to tDCS (e.g., implants or metal near the head), and prior unsuccessful treatment with tDCS, ECT, >15 rTMS sessions, or >4 ketamine sessions. The use of benzodiazepines exceeding lorazepam 2 mg/day, dermatological conditions contraindicating tDCS, non-correctable sensory impairments, or inability to consent or participate as an outpatient also disqualify candidates.

Screening

Informed consent will be obtained at this visit, preceding any study-related procedures. Study personnel will address any questions or concerns participants may have prior to consent acquisition. Participants will receive a copy of their signed consent form, while the original will be kept by the investigators. Participants will also sign the Study Equipment Care Agreement at that time. Screening assessments will encompass demographic details, medical history, current and lifetime ATHF-SF information, and concomitant medication usage. Additionally, participants will undergo the Mini-International Neuropsychiatric Interview (MINI), the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR), PHQ9, the MADRS, and the Modified Scale for Suicidal Ideation (MSSI). A review of potential adverse events associated with tDCS will be performed to ascertain if participants are already experiencing any of those symptoms at baseline, helping to distinguish between pre-existing conditions and any effects potentially attributable to the treatment. Individuals of childbearing potential will be required to confirm that they are not pregnant by a negative result from a pregnancy test supplied by the study team. Lastly, each potential participant will test the tDCS procedure at 2 mA intensity for 2 minutes to ascertain tolerability. If the participant completed the screening visit remotely they will test the tDCS procedure at 2 mA intensity for 2 minutes to ascertain tolerability and complete a pregnancy test. The pregnancy test will be completed prior to the tDCS tolerability test. This screening visit will last approximately 3 hours. If the screening visit is completed via UCSD telehealth, consent will be obtained via UCSD DocuSign.

California law provides specific rights when participants are asked to provide electronic consent:

- Participants will have the right to obtain a copy of the consent document in a non-electronic format.
- Participants will have the right to provide consent in a non-electronic format.
- If the participant changes their mind about electronic consent, they have the right to request their electronic consent to be withdrawn and can be provided consent in a non-electronic format; however, a copy of the electronic consent will be maintained for regulatory purposes. If the participant wishes to withdraw their electronic consent they must tell the study team.
- This agreement for electronic consent applies only to the participants consent to participate in this research study.

Pre-treatment measures

The pre-treatment visit will consist of both baseline clinical assessments and neurophysiology procedures. The baseline clinical assessment will include a review of any concomitant

medications, and participants will complete the MADRS, PHQ-9, and QIDS-SR. Neurophysiological measures will include TMS-EEG, TMS-EMG and rsEEG. Baseline neurophysiological data will need to be collected within 10 days of the start of treatment. This visit will last approximately 2.5 to 3 hours, with 30 minutes allocated for clinical assessments, 1 hour for TMS-EEG procedures, 1 hour for TMS-EMG procedures, and 10 minutes for rsEEG procedures.

Neurophysiological assessment procedures details: During the neurophysiology visits, TMS-EEG, TMS-EMG and rsEEG will be conducted. TMS-EEG procedures will involve the DLFPC and TMS-EMG the motor cortex. These protocols include, if time permits, single pulse and paired pulse, such as intracortical facilitation (ICF), short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and cortical silent period (CSP) (for TMS-EMG only).

TMS-EEG over DLPFC will measure TMS-evoked potentials (TEPs), providing insights into cortical reactivity and network connectivity. TMS-EMG over the motor cortex will assess motor-evoked potentials (MEPs) and include single- and paired-pulse paradigms. SICI and LICI measure GABA-A and GABA-B–mediated inhibitory activity, respectively, while ICF assesses glutamatergic excitability. The CSP reflects GABA-B-mediated inhibitory processes. These paradigms collectively allow for a comprehensive assessment of excitatory-inhibitory balance and synaptic plasticity mechanisms engaged by tDCS.

For rsEEG, we will perform two EEG recordings of 5 minutes while the participant is at rest. In one recording, the participant will be instructed to keep their eyes open, and in the other one closed. This neurophysiology sessions visit will take place over about 2.5 to 3 hours on the same day.

If the participant completed the screening visit remotely they will test the tDCS procedure at 2 mA intensity for 2 minutes to ascertain tolerability and complete a pregnancy test.

Trial design
This will be a pilot, prospective, single-arm, open-label feasibility study. Treatment will be delivered over a 2-week period with daily weekday treatments. Participants will self-administer treatment at home under direct remote supervision. Participants will follow-up with the study team up to 3 months after treatment to capture long term effects.

Treatment Phase
Participants will receive treatment daily on weekdays over two consecutive weeks (10 sessions total). The first treatment will occur in-clinic and will include comprehensive hands-on training in device setup, electrode placement, safety procedures, and session initiation under direct supervision, ensuring participants can independently and safely self-administer tDCS at home. All subsequent sessions will be conducted at home under real-time remote supervision by a trained clinical research coordinator (CRC) via Microsoft Teams or Zoom. Each treatment day will last approximately three hours. Monitoring of adverse events, skin irritation, and concomitant medication use will occur throughout the treatment phase. Participants may begin treatment on any weekday (preferably Monday) and are expected to attend daily sessions until completing the required 10 treatments. If discomfort or side effects occur, participants may skip treatment days as needed, provided they receive a minimum of two sessions per week. The acute treatment phase must be completed within a maximum of four weeks. Participants will complete MADRS, PHQ-9 and QIDS-SR assessments at the end of treatment days 5 and 10.

Follow-up visits

Post-treatment follow-up visits will occur at 1, 2, 3, 4, 8, and 12 weeks after the final treatment session. At each visit, concomitant medications and adverse events will be reviewed, and participants will complete the MADRS, PHQ-9, and QIDS-SR. The 1- and 4-week follow-ups will be conducted in-clinic to allow for post-treatment neurophysiological reassessment (approximately 3 hours). All other follow-up visits will be conducted remotely and will last approximately 30 minutes.

3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This open-label feasibility study is designed to evaluate the safety, tolerability, and preliminary efficacy of a home-based, spaced tDCS protocol for treatment-resistant depression (TRD). The spaced stimulation approach—delivering multiple sessions with short inter-session intervals—is grounded in preclinical and human neurophysiology research demonstrating its ability to enhance late-phase long-term potentiation (LTP) and promote more sustained neuroplastic changes compared to single-session paradigms. Given that TRD is characterized by impaired neuroplasticity, optimizing tDCS delivery to better engage plasticity mechanisms is a key therapeutic goal.

This initial open-label study serves as a necessary precursor to a future randomized, controlled trial by allowing for real-world testing of device setup, remote supervision procedures, and participant adherence in a home setting. The home-based, remotely supervised model is designed to overcome key scalability limitations of conventional interventional treatments such as rTMS and ECT, offering a low-cost, accessible, and patient-centered alternative while maintaining rigorous safety oversight through live monitoring.
Neurophysiological assessments using TMS-EEG, TMS-EMG, and rsEEG will enable evaluation of cortical excitability, inhibitory/excitatory balance, and resting-state dynamics. These objective measures will support exploration of tDCS-induced neural changes and identify markers that may predict treatment response in future trials.

Overall, this study provides critical feasibility and mechanistic data needed to support a larger, sham-controlled trial of home-based spaced tDCS for TRD, with the long-term goal of enabling scalable, personalized neuromodulation interventions.

3.3 JUSTIFICATION FOR DOSE

The selected 2 mA, 20-minute spaced tDCS protocol is based on clinical and neurophysiological evidence optimizing efficacy, safety, and tolerability. A 2 mA intensity is widely used in depression studies with proven antidepressant effects and minimal side effects. Spaced stimulation, with multiple sessions separated by short intervals, enhances late-LTP and maximizes neuroplasticity engagement, addressing TRD's severe plasticity deficits. The 2-week treatment period is the same as used in our previous clinic-based study.

3.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if they have completed all phases of the study shown in the Schedule of Activities (SoA).

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. People between the ages of 18 and 85 at the time of screening.
2. Able to read, understand, and provide written, dated informed consent prior to screening. Proficiency in English sufficient to complete questionnaires / follow instructions during interventions. Stated willingness to comply with all study procedures, including availability for the duration of the study, and to communicate with study personnel about adverse events and other clinically important information.
3. Currently diagnosed with Major Depressive Disorder (MDD) and meets criteria for a Major Depressive Episode, according to the criteria defined in the Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5).
4. Medical records confirming a history of at least moderate treatment-resistance as defined on Antidepressant Treatment History Form (ATHF) score for that antidepressant trial of > 2 in the current episode OR have been unable to tolerate at least 2 separate trials of antidepressants of inadequate dose and duration (ATHF score of 1 or 2 on those 2 separate antidepressants) OR have a combination of one failed trial and one not tolerated trial, per the definitions above.
5. MADRS score of ≥20 at screening.
6. Existing relationship with mental health provider and access to ongoing psychiatric care before and after completion of the study.
7. Must be on a stable antidepressant therapeutic regimen for at least 4 weeks prior to study enrollment and agree to continue this regimen throughout the study period. Participants who are not currently on antidepressant treatment are eligible, provided that no discontinuation occurred within the 4 weeks preceding study enrollment.
8. In good general health, as evidenced by medical history.
9. For persons of child-bearing potential: use of highly effective contraception for at least 1 month prior to screening and agreement to use such a method during study participation.
10. Agreement to adhere to Lifestyle Considerations (i.e. must continue with any existing treatments) throughout study duration.
11. For persons of child-bearing potential: must take a pregnancy test prior to the tDCS tolerability test, with results confirmed as negative by study staff.
12. Participants will need to have a stable internet connection and a device compatible with Microsoft Teams or Zoom to facilitate remote communication and engagement in study activities.

4.2 EXCLUSION CRITERIA

An individual will be excluded from participation in this study if they meet any of the following criteria, as determined from a review of medical records prior to screening or at the screening visit:

1. Pregnancy this includes breastfeeding or trying to becoming pregnant.
2. History of psychotic or bipolar disorder or depression with psychotic features.
3. Significant borderline personality disorder.
4. Significant comorbid obsessive-compulsive or post-traumatic stress disorder.
5. Previously diagnosed Intellectual Disability or Autism Spectrum Disorder.
6. Current moderate or severe substance use disorder or demonstrating signs of acute substance withdrawal.

7. Clinically significant suicidality.
8. Any history of tDCS.
9. Any history of ECT.
10. History of TMS (greater than 15 sessions) without a clinically meaningful response.
11. History of ketamine (greater than 4 sessions) without a clinically meaningful response.
12. Chronic depression (defined as of over 5 years duration).
13. History of significant neurologic disease, including dementia, Parkinson's or Huntington's disease, brain tumor, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma with persistent symptoms.
14. Untreated or insufficiently treated endocrine disorder.
15. Contraindication to receiving tDCS (e.g., ferromagnetic implant, history of seizure, known brain lesion).
16. Treatment with an investigational drug or other intervention within the study period.
17. Unstable symptoms between screening and baseline as defined by a ≥ 30% change in MADRS score.
18. Require a benzodiazepine with a dose > lorazepam 2 mg/day
19. Has started a new psychotherapeutic process in the past 3 months from screening.
20. Use of potentially irritant topical treatments (ex: retinoids, alpha hydroxy acids).
21. Aesthetic procedure on the area of the forehead directly below the stimulation area within the last 6 months (laser, fillers, surgery, etc.).
22. Any active dermatological condition on face or scalp that would in the opinion of the PI represent a contraindication to the treatment.

Discontinuation Criteria

Participants will be discontinued from the treatment if they cannot continue the study safely based on any of the following criteria:

1. Experience worsening in depression, defined as an increase in MADRS score from baseline of more than 30% on two consecutive assessments.
2. Experience clinically significant increase in suicidal ideation with imminent or attempted suicide.
3. Withdraw consent.
4. Non-compliant with treatment schedule (i.e., number of missed treatments fall outside of protocol boundaries).
5. The Principal Investigator (PI) believes that for safety reasons, it is in the best interest of the participant to stop participation.
6. The participant becomes pregnant.
7.

4.3 LIFESTYLE CONSIDERATIONS

Patients will not be asked to discontinue their outside treatment. There is no evidence suggesting that compounding treatments may worsen depressive symptoms.

4.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of current depressive symptoms or treatments may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Name of Device	Manufacturer	Marketing Status in the US	FDA device Classification (1, 2, 3)
Soterix Medical mini-CT	Soterix	IDE	2

5.1.2 DOSING AND ADMINISTRATION

tDCS sessions will be self-administered at home under the supervision of a trained clinical research coordinator (CRC) using the Soterix Medical mini-CT device (Soterix, New York, USA) with remote monitoring via a secure videoconferencing platform (e.g., Microsoft Teams, Zoom). The mini-CT device is designed for safe, remote tDCS delivery, and all session data, including compliance and impedance levels, will be logged. On the first treatment day, participants will visit the clinic to receive the equipment and undergo training in safe and effective device use. During home sessions, participants will program the device using a code provided by a staff member. Each treatment day will consist of five tDCS sessions, each lasting 20 minutes, spaced by approximately 20-minute inter-session intervals, for a total of three hours per day. Participants will log in to Microsoft Teams or Zoom and complete each session under continuous CRC supervision. Participants in the active spaced tDCS group will receive stimulation at 2 mA, with a 30-second ramp-up and ramp-down phase. The tDCS devices will not display treatment details. Saline pre-saturated (0.9%) 5×5 cm disposable “SNAPpads” sponge electrodes will be used and replaced for each session. Electrodes will be positioned over the left and right DLPFC using the “SNAPstrap” or “SNAPheadset” systems (F3/F4, international 10-20 EEG system). Treatment will only proceed if contact quality is rated as “good.” Electrode position and impedance levels will be monitored and maintained throughout stimulation. Daily impedance data will be collected, and remote skin inspections will be conducted before and after each session. Participants will be instructed to avoid applying creams or makeup before sessions and to cleanse the skin with mild soap, avoiding abrasive methods.

5.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

5.2.1 ACQUISITION AND ACCOUNTABILITY

All interventional devices will be owned, stored, and managed by the Interventional Psychiatry Program at the University of California San Diego (IPP-UCSD). tDCS devices will be loaned to participants for home use under remote supervision. Devices are provided on a temporary basis and remain the property of the study team. Participants are expected to use the equipment appropriately and return it at the end of the study. While participants will not be held financially responsible for loss, theft, or accidental damage, they will be required to report any such incidents immediately. These terms are outlined in the Study Equipment Care Agreement, which all enrolled participants must sign prior to device allocation.

5.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Equipment will be owned and set up by the IPP-UCSD. Trained staff will check and prepare the devices as needed throughout the study.

5.2.3 PRODUCT STORAGE

When not in use, all devices will be stored behind locked doors with access restricted to members of the IPP-UCSD. During the intervention period, participants will be instructed to store the device in a secure location within their home, such as a locked drawer or cabinet, out of reach of children and other household members. These storage instructions will be reviewed during the initial training session and reinforced in the Study Equipment Care Agreement to ensure proper handling and restricted access throughout the study. Devices will continue to be stored and maintained in accordance with manufacturer requirements.

5.2.4 PREPARATION

Participants will be instructed not to apply any cream or make-up before the procedure, and to gently clean the skin to be exposed to the electrodes before treatment using a mild soap, avoiding abrasive methods. This will be confirmed with the participant before each treatment day. The "SNAPpads" sponge-electrodes delivering the stimulation are held in place by "SNAPstrap" headsets, allowing reliable positioning (F3/F4, international 10-20 EEG system). Once the headset is in place, participants will activate the stimulator, and the session will start. Once the session ends, the headset will be removed, and the stimulator turned off.

5.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A - This is an open-label trial without randomization or masking.

5.4 STUDY INTERVENTION COMPLIANCE

Trained staff will supervise tDCS treatment remotely and monitor patients throughout treatment. They will use a standard operating procedure to ensure study compliance, including tracking the necessary tDCS sessions. Research coordinators are certified to administer tDCS treatments once they have completed operator training and have been cleared by the study PI, Dr. Miron.

5.5 CONCOMITANT THERAPY

For this protocol, patients may have an existing treatment regimen outside of the trial. Prior to enrolling, patients will be asked about any outside treatments and must have been enrolled in their treatment for at least 4 weeks prior to completing the baseline for this trial. This will be confirmed during screening visits as well. Patients will be asked to continue their same treatments during study participation.

5.5.1 RESCUE MEDICINE

N/A - This study will not supply rescue medication.

6 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

N/A – Patients are not able to remain in the trial without enrolling in the treatment. Discontinuation from the tDCS will mean discontinuation from the study. Ending tDCS due to adverse events will be documented, and patient will be evaluated for safety.

6.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Participants will be discontinued from the treatment if they cannot continue the study safely based on any of the following criteria:

1. Experience worsening in depression, defined as an increase in MADRS score from baseline of more than 30% on two consecutive assessments;
2. Experience clinically significant increase in suicidal ideation with imminent intent (based on the MSSI) or attempt suicide;
3. Develop clinically significant hypomanic or manic symptoms;
4. Withdraw consent;
5. Non-compliant with treatment schedule;
6. The PI believes that for safety reasons, it is in the best interest of the participant to stop participation;
7. The subject becomes pregnant.

We anticipate that some participants may withdraw. We do not expect early termination of participation due to patient or investigator withdrawal to have any impact on safety or well-being of participants. Patients who withdraw for adverse events will be evaluated by trained staff for safety. Participants who enroll in the study (i.e., sign consent and pass screening) and are subsequently withdrawn will be replaced.

6.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they fail to return for a scheduled visit and/or are unable to be contacted by the study site staff. If a participant fails to appear for a scheduled visit, staff will attempt to contact and reschedule if the participant wishes and is able to continue in the study. Staff will reach out at least three times via phone, email, or text. If the participant remains unreachable, they will be designated as lost to follow-up. In such cases, the study team will make additional attempts to retrieve the study device, including sending a formal written request and offering pre-paid, pre-labeled return packaging. If no response is received, and if previously consented, a courier pickup may be arranged. If retrieval remains unsuccessful, the unreturned equipment will be documented and reported to the PI, but no further action will be taken to avoid infringing on participant rights.

6.4 PARTICIPANT COMPENSATION

Compensation will be provided in the form of a Vanilla Visa gift card. Participants can receive a maximum of $60 for completing all trial-related activities, with $20 for each neurophysiology visit. Payment will be made after each neurophysiology visit.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 EFFICACY ASSESSMENTS

Efficacy will be determined by score changes pre- and post-treatment (baseline to last treatment day) on the MADRS.

7.2 SAFETY AND OTHER ASSESSMENTS

Screening assessments will include demographic and medical history, concomitant medications recording, MINI, ATHF, TASS, MADRS, QIDS-SR, PHQ-9, and MSSI. Patients will be monitored daily for adverse events and directly queried about symptoms such as headache, tingling or burning sensations at the stimulation site, dizziness, fatigue, insomnia, anxiety, nausea, and phosphenes. Skin condition under the electrodes will also be monitored daily before, during, and after each treatment session and at follow-up. In addition to general adverse event monitoring, depression severity will be specifically assessed using the MADRS, PHQ-9, and QIDS-SR at regular intervals, including after sessions 5 and 10, and at each follow-up. If scores on these measures indicate worsening depression or emerging suicidality, the case will be immediately escalated to the PI or study clinician for evaluation. Crisis protocols will be activated if necessary, including referral to the participant's primary mental health provider, direct clinical assessment, or emergency intervention. Participants with clinically significant suicidal ideation will be withdrawn from the study and referred for appropriate care.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as AEs. A pre-existing condition should be recorded as an AE if the frequency, intensity, or the character of the condition changes.

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event (SAE) is any AE that is:

- Fatal;
- Life-threatening;
- Requires or prolongs hospital stay;
- Results in persistent or significant disability or incapacity;
- A congenital anomaly or birth defect;
- An important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes;
- Required intervention to prevent permanent impairment or damage (for devices only).

Important medical events are those that may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse,

a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

7.3.3 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

An UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3.4 CLASSIFICATION OF AN ADVERSE EVENT

7.3.4.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol-defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

7.3.4.2 RELATIONSHIP TO STUDY INTERVENTION

All AEs must have their relationship to the tDCS administration assessed by the PI. The degree of certainty about causality will be graded using the categories below:

- Definitely Related – There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- Unlikely to be related – A clinical event whose temporal relationship tDCS administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of tDCS administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.3.4.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for tDCS.

7.3.5 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Safety will be assessed by monitoring and recording potential adverse effects at each study visit. Information on all AEs will be recorded in the source documentation. To the extent possible, each AE or follow-up information will be evaluated by the PI. This allows the site to determine the relationship to treatment, expectedness, and seriousness of the event. It also allows the site to evaluate patient safety and work with the patient to a resolution.

7.3.6 ADVERSE EVENT REPORTING

AEs will be recorded from the time of informed consent until study completion. The PI will evaluate all SAEs to determine whether they are unexpected, related to the device, and suggest that the research presents greater risk than previously recognized. Only those SAEs meeting this threshold will be reported to the IRB. In the event of an unanticipated adverse device effect (UADE), the investigator will complete an Unanticipated Adverse Device Effect Form and submit it to the IRB as soon as possible, but no later than 10 working days after first awareness. As the sponsor, the PI is also responsible for evaluating the UADE and reporting the findings to both the FDA and the IRB within 10 working days of receiving notice, with additional reports submitted to the FDA as requested.

7.3.7 SERIOUS ADVERSE EVENT REPORTING

SAEs will be reported to the IRB.

7.3.8 REPORTING EVENTS TO PARTICIPANTS

AEs (both individual and aggregate level) will be shared with participants as the PI finds necessary.

7.3.9 EVENTS OF SPECIAL INTEREST

Notable events, such as device malfunctions, will be documented and reported as needed.

7.3.10 REPORTING OF PREGNANCY

All people of childbearing potential must take a pregnancy test, confirmed negative by study personnel, before beginning this research study. The research team will provide the test. Participants for whom pregnancy is a possibility are required to use effective contraception throughout their participation. Acceptable methods include hormonal contraceptives, double-barrier methods, or abstinence. Participants will also attest to not being pregnant on the TMS safety screening form. Due to potential safety concerns, pregnant individuals will not be eligible to participate, and any participant who becomes pregnant during the study will be withdrawn immediately. Pregnancy will be documented in the study records and reported to the IRB. Participants who indicate no possibility of pregnancy (e.g., due to menopause, surgical

sterilization, or abstinence) may be exempt from pregnancy testing with appropriate documentation.

7.4 UNANTICIPATED PROBLEMS

7.4.0 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB/ACT Health HREC-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.4.1 UNANTICIPATED PROBLEM REPORTING

Unanticipated problems should be reported by the PI to the necessary regulatory groups within the timeline required by local regulations.

7.4.2 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Unanticipated problems (both individual and aggregate level) will be shared with participants as the PI finds necessary.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

Primary analysis
The primary analysis will be descriptive and exploratory, focusing on feasibility (recruitment, retention, and adherence rates), safety (incidence of serious adverse events), and tolerability (frequency and severity of reported side effects). Preliminary efficacy will be assessed by evaluating changes in depressive symptoms using the Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to end of treatment (day 10). Paired t-tests (or non-parametric alternatives, such as the Wilcoxon signed-rank test, if normality is violated) will be used to compare pre- and post-treatment MADRS scores. Effect sizes (Cohen's d) will be calculated to estimate the magnitude of symptom change. These results will be used to inform the design, power calculations, and outcome selection for a subsequent randomized controlled trial.

8.2 SAMPLE SIZE DETERMINATION

No single guideline exists for pilot studies sample size calculations, with recommendations varying from 12 participants per group [98], 30 participants per group [99], 10 to 40 participants per group [100,101] or at least 9% of the main trial's sample size [102]. For the purposes of this study, a sample of 10 participants was selected as it balances the need to assess feasibility, safety, and tolerability in a tightly controlled, resource-constrained home-based protocol while minimizing participant risk. This sample size is sufficient to evaluate procedural adherence, remote supervision logistics, and adverse event rates, which are the primary goals of this feasibility study. Findings will guide protocol refinement and inform power calculations for a subsequent larger randomized controlled trial.

8.3 POPULATIONS FOR ANALYSES

All participants who receive at least one tDCS session will be included in the safety and tolerability analyses (safety population). Analyses of clinical outcomes will be conducted in participants who complete at least 5 of the 10 scheduled treatment days and have both baseline and post-treatment symptom assessments. Exploratory neurophysiological analyses will be limited to participants with complete and analyzable data at the specified time points.

8.4 STATISTICAL ANALYSES

8.4.0 GENERAL APPROACH

Baseline patient characteristics will be summarized using descriptive statistics (e.g., means, standard deviations, proportions) and presented in tabular form.

8.4.1 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoints are three-fold, as follows: (i) recruitment, retention, and protocol adherence; (ii) safety; and (iii) tolerability. Recruitment will be qualitatively assessed as having met (or not) the predetermined participant counts within the study timeframe. Retention rates will be defined as the proportion of patients not lost to follow-up by the end of the final assessment. Protocol adherence will be defined as the proportion of total visits attended. Safety, defined as the number of SAEs. Tolerability will be determined by comparing the incidence of AEs that meet the PI’s criteria for “Possibly Related,” “Probably Related,” or “Definitely Related” to the intervention within event severity categories (e.g., mild, moderate, severe).

8.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The MADRS, a 10-item clinician-administered scale measuring depressive symptom severity (range: 0–60), will serve as the primary clinical outcome for exploratory purposes. Given the small sample size and single-arm design, changes in MADRS scores from baseline to post-treatment (day 10) and follow-up will be summarized descriptively. Within-subject comparisons over time may be explored using paired tests or linear mixed-effects models, recognizing the limited power to detect significant effects. Effect sizes (e.g., Cohen’s d) will be estimated to inform the design and power calculations of future controlled trials. Analyses will be strictly exploratory and hypothesis-generating.

8.4.4 SAFETY ANALYSES

N/A

8.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline patient characteristics (e.g., age, sex, MADRS, HAMD, QIDS-SR, PHQ-9, MSSI, and EEG parameters) will be summarized using descriptive statistics (e.g., means, standard deviations, proportions) and compared with nonparametric Fisher's exact tests or Kruskal-Wallis tests for categorical and continuous variables, respectively.

8.4.6 PLANNED INTERIM ANALYSES

N/A

8.4.7 SUB-GROUP ANALYSES

N/A

8.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

For the purposes of all proposed analyses, which necessitate within- and between-subjects longitudinal comparisons, participant data will be tabulated by measure and timepoint.

8.4.2 EXPLORATORY ANALYSES

Neurophysiological exploratory endpoints include continuous measures derived from resting-state EEG and TMS-evoked potentials, reflecting cortical excitability and functional connectivity. These measures are expressed in arbitrary units and are expected to follow a Gaussian distribution; if substantially skewed, appropriate transformations will be applied. As this is an exploratory, single-arm study, within-subject changes over time will be analyzed using linear mixed-effects models, with time as a fixed effect and subject as a random effect. Covariates such as age, sex, and baseline depression severity may be included to explore their influence on neurophysiological trajectories. Effect sizes will be reported for changes at each post-intervention time point relative to baseline. Associations between changes in depressive symptom scores (e.g., MADRS) and changes in neurophysiological measures will be explored using within-subject correlation models or generalized estimating equations (GEE), where appropriate. Given the multiplicity of neurophysiological endpoints, p-values will be adjusted using false discovery rate (FDR) correction to control for Type I error inflation. These analyses are exploratory and intended to inform biomarker selection and hypothesis generation for future controlled studies.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.0 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated by the PI if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule. The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or FDA.

9.1.1 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI. All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), regulatory agencies or the device company supplying the study devices may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and institutional policies' requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored to IRB compliant online databases, such as REDCap. PHI will be stored separately in secure cabinets inside locked rooms. Coded data will be stored on a secure server at the University of California through the Neuroscience Neuroimaging Group computing cluster. Coded data are directly uploaded to the computing cluster from the computers on which the data are collected. The UCSD computers are in a secured lab space and connected directly to the UCSD encrypted network. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected.

9.1.2 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored to IRB compliant online databases, such as REDCap. De‐identified data may be shared with other investigators, with a formal data‐sharing agreement.

9.1.3 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor.

Principal Investigator	**Medical Monitor**
Jean-Philippe Miron, MD, PhD, FRCPC	Cory Weissman, MD
University of California San Diego	University of California San Diego
9500 GILMAN Drive #0603 La Jolla, CA 92093-0603	9500 GILMAN Drive #0603 La Jolla, CA 92093-0603
(858) 534-5821	(858) 534-5821
mironjp@health.ucsd.edu	cweissman@health.ucsd.edu

9.1.4 SAFETY OVERSIGHT

Subject safety will be closely monitored. Subjects reporting side effects will be used to evaluate individual safety of tDCS. The PI will be monitoring the ongoing safety of subjects. PI is responsible for monitoring the data quality and the ongoing safety of subjects at respective sites.

9.1.5 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable and that the conduct of the trial follows the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Physician monitoring of symptoms and treatment response will occur in conjunction with all study procedures to assure participant well-being, intervene in the event of an emergency, and adjust the treatment course if necessary.

9.1.6 DATA HANDLING AND RECORD KEEPING

Data collection is the responsibility of site under the supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and follow ALCOAC standards (attributable, legible, contemporaneous, original, accurate, and complete). Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents. Study documents will be retained for the necessary time, as required by local regulations.

9.1.7 PROTOCOL DEVIATIONS

The PI and the study team should document all scenarios where the protocol is not followed. They should assess whether the deviation is considered of significant impact (such as increasing risks to participants, etc.) and should be reported as required, with suggestions for corrective plans to prevent such occurrences.

9.2 ADDITIONAL CONSIDERATIONS

Abbreviations/Acronyms

AE	Adverse Event
ATHF	Antidepressant Treatment History Form-Short Form
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DLPFC	Dorsolateral Prefrontal Cortex
DSM-5	Diagnosis and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
eCRF	Electronic Case Report Forms
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAMD	17-item Hamilton Rating Scale for Depression
HIPAA	Health Insurance Portability and Accountability Act
HRE	Human Research Ethics
HREC	Human Research Ethics Committee

ICH	International Conference on Harmonization
IPP-UCSD	Interventional Psychiatry Department at University of California San Diego
IRB	Institutional Review Board
MADRS	Montgomery Åsberg Depression Rating Scale
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MSSI	Modified Scale for Suicide Ideation
NCT	National Clinical Trial
NIH	National Institutes of Health
PI	Principal Investigator
PHQ-9	Patient Health Questionnaire - 9
QIDS-SR	Quick Inventory Depression Scale – Self Report
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SOA	Schedule of Activities
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TASS	Transcranial Magnetic Stimulation Adult Safety Screening
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
TRD	Treatment-Resistant Depression
UCSD	University of California San Diego

Protocol Amendment History
The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
2.1	10/13/2025	Added Zoom telehealth technology as an option of remote supervision.	Allow for any IRB approved telehealth technology i.e., Teams and Zoom to give participants the option to choose which one they are more comfortable using.
2.1	10/13/2025	Added PHQ-9	Assessment of depressive symptoms that provides additional information on participants status via this short questionnaire.
2.2	10/31/2025	Screening visit can be conducted remotely via UCSD Zoom/Teams telehealth technology. Due to this change, the tDCS tolerability test and pregnancy test can be completed at visit 2 which will occur in person The pregnancy	This will help with recruitment as this would be 1 less visit that the participant has to attend in person.

		test will be completed first before testing the tDCS device.	
2.2	10/31/2025	Added clinical trials # to the first page	This study is now public on clinicaltrials.gov so we entered the ID number on the first page of this protocol

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