Cover Page

Official Study Title
Remotely Supervised Transcranial Direct Current Stimulation for Slowing Disease Progression in Amyotrophic Lateral Sclerosis (ALS)

NCT Number
NCT04866771

Document Type
Study Protocol and Statistical Analysis Plan

Document Date
January 1, 2023

Sponsor
University of Illinois at Chicago

Principal Investigator
Dr. Sangeetha Madhavan, PT, PhD
Professor, Department of Physical Therapy
University of Illinois at Chicago

Remotely Supervised Transcranial Direct Current Stimulation for Slowing Disease Progression in Amyotrophic Lateral Sclerosis (ALS)

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

10MWT	10-meter walk test (10MWT)
AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
ANOVA	Analysis of Variance
BBS	Berg's Balance Scale
EMG	Electromyogram
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LMN	Lower Motor Neuron
M1	Primary Motor Cortex
MEP	Motor Evoked Potential
MS	Multiple Sclerosis
NSE	Neuron Specific Enolase
NIBS	Non-invasive Brain Stimulation
PI	Principal Investigator
PNS	Peripheral Nerve Stimulation
RCT	Randomized Control Trial
RPE	Rate of Perceived Exertion
RS-tDCS	Remotely Supervised Transcranial Direct Current Stimulation
TA	Tibialis Anterior
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
UMN	Upper Motor Neuron
UIC	University of Illinois at Chicago

1.0 Project Summary/Abstract

ALS affects as many as 30,000 individuals in the United States, with 5,600 new cases diagnosed each year. Riluzole and edaravone, the only drugs approved by the U.S. FDA for ALS, slow ALS progression; however, they do not demonstrate marked improvement in ALS symptoms and increase survival time only by a few months. Hence, most of the care is centered on patient support and symptom management, making rehabilitation an integral aspect for slowing disease progression, prolonging life span and increasing quality of life. Our long-term goal is to develop neuromodulation therapies for easy clinical management of ALS. Transcranial direct current stimulation (tDCS) has been increasingly explored as a promising neuromodulatory tool to prime motor function in several neurological disorders. Despite the emerging importance of cortical dysfunction as a pathophysiological biomarker in disease progression, the study of tDCS in ALS is limited. Here we propose a novel mechanism using remotely supervised tDCS (RS-tDCS) to target hypoexcitable neural pathways to preserve motor function in individuals with ALS. Due to its low risk, ease of use, and portability, tDCS is a candidate neuromodality to be administered in a home-based environment with remote supervision from qualified personnel. Remote supervision would ensure that the stimulation is delivered optimally in the comfort of a patient's home, reducing burden on patients and caregivers to travel to the clinic or research facility and encourage protocol adherence. We aim to investigate the effectiveness and feasibility of long-term RS-tDCS in individuals with ALS. In a delayed-start design, 100 participants with ALS will be randomized into remotely supervised tDCS or delayed-start control group. The intervention group will receive 24 weeks of anodal tDCS (3 times/week; 72 sessions). The delayed-start group will first receive sham tDCS for 12 weeks followed by a switch to anodal tDCS for 12 weeks. Aim 1 will investigate the safety and feasibility of long-term treatment with anodal RS-tDCS in ALS. Aim 2 will determine the effects of 24-weeks of RS-tDCS on disease progression in individuals with ALS, using the ALS Functional Rating Scale (Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.

As a secondary aim, we will explore the effectiveness of RS-tDCS on upper and lower motor neuron mechanisms in individuals with ALS, quantified using Upper and lower motor neuron mechanisms will be assessed using single-pulse transcranial magnetic stimulation (TMS).

Successful completion of this project will trigger future studies that will test the clinical translation of tDCS as a home-based neuromodulatory adjuvant to slow disease progression in ALS and create a paradigm shift in the clinical management of ALS.

Hence, the objectives of this pilot study are:

- Aim 1: To investigate the safety and feasibility of long-term treatment with anodal RS-tDCS in ALS.
- Aim 2: To determine the effects of 24-weeks of RS-tDCS on disease progression in individuals with ALS, using the ALS Functional Rating Scale (Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.

- Aim 3: To determine the effects of RS-tDCS on upper (UMN) and lower motor neuron (LMN) mechanisms in individuals with ALS, quantified using Upper and lower motor neuron mechanisms will be assessed using single-pulse transcranial magnetic stimulation (TMS).

2.0 Background/Scientific Rationale

Amyotrophic Lateral Sclerosis (ALS): ALS is a rapidly progressive neurodegenerative disorder that causes muscle weakness, and eventually death from respiratory failure (Borasio & Miller, 2001). Glutamate mediated excitotoxicity has been implicated as a predominant cause for neuronal cell death in ALS (Steve Vucic, Ziemann, Eisen, Hallett, & Kiernan, 2012). Integrity of the glutamatergic circuits can be non-invasively assessed via TMS. Several lines of evidence have implicated the degeneration of corticospinal neurons via glutamate excitotoxicity, followed by that of lower motor neurons as the pathophysiological site of disease onset in ALS (Attarian, Pouget, & Schmied, 2009; Floyd et al., 2009; Geevasinga, Menon, Kiernan, & Vucic, 2014; Steve Vucic et al., 2012). Few TMS studies have established motor cortical and corticospinal dysfunction in ALS, with cortical hyperexcitability being an early feature in sporadic forms of ALS and preceding the clinical onset of familial ALS (S. Vucic, Cheah, Yiannikas, & Kiernan, 2011; Steve Vucic et al., 2012). Other non-invasive therapeutic adjuncts such as repetitive TMS or Transcranial Direct Current Stimulation (tDCS) are currently being investigated based on the evidence garnered from TMS based studies.

tDCS: tDCS is a therapeutic adjunct that has emerged as a promising tool to modulate neural excitability and enhance motor learning and motor behaviour ALS (Boggio et al., 2007; Fleming, Pavlou, Newham, Sztriha, & Teo, 2016; Lefaucheur, 2016; M. A. Nitsche et al., 2008; Michael A Nitsche, Kuo, Paulus, & Antal, 2015; Schlaug & Renga, 2008; Ziemann & Eisen, 2004). tDCS involves the application of low intensity direct current to the scalp, and although it does not directly induce action potentials, it alters the membrane potentials that affect neuronal excitability (Stagg & Nitsche, 2011). Stimulation with the anode over the motor cortex contralateral to the target muscles and the cathode over the ipsilateral orbit (anodal tDCS) increases the excitability of the corticospinal projections to the target muscle (Stagg & Nitsche, 2011). In contrast, with the cathode over the motor cortex and the anode over the orbit (cathodal tDCS), corticospinal excitability is decreased. tDCS has been shown to be effective as a neuromodulatory adjunct in stroke, Parkinson's disease, Multiple Sclerosis and several other neurological disorders (Palm, Ayache, Padberg, & Lefaucheur, 2014)

Transcranial direct current stimulation (tDCS) is one of the technically uncomplicated NIBS protocols to apply. During tDCS, electrodes are placed and secured to the scalp over the desired areas and currents are delivered to the underlying cortical tissue. The stimulation elicits minimal discomfort and only a mild tingling sensation that usually disappears after a few seconds (M. A. Nitsche & Paulus, 2000). By varying the position and polarity of the electrodes, tDCS has been adapted to produce a wide variety of effects (Kantak et al., 2010; Kessler, Turkeltaub, Benson, & Hamilton, 2012; Reis et al., 2009). There is evidence that anodal (facilitatory) tDCS applied over M1 during skilled task performance in healthy subjects enhances hand motor skill acquisition with persistence of the beneficial effect 3-months after training (Reis et al., 2009). tDCS has been evaluated as a viable clinical adjuvant therapy in those with ALS (Munneke et al., 2011; Quartarone et al., 2007). tDCS session are typically administered for four weeks (3 times/week

for 12 sessions). The number of sessions are dictated in part by patient convenience as patient adherence to the study drops if longer time periods are necessitated. Also, many participants are unable to travel to the laboratories to obtain the benefits of lab based tDCS. Given that tDCS is a safe procedure, tDCS treatment can be administered outside the laboratory under remote supervision. The participants would be educated and trained by the research team in tDCS treatment and electrode preparation techniques. A remotely supervised tDCS treatment would potentially increase patient compliance.

Safety of tDCS: The relatively low cost of tDCS devices along with the potential beneficial effects combined with its safe, simple, painless application and easy portability, makes it an ideal candidate to be used as a clinical adjuvant before or during therapy to enhance neuroplastic changes and improve function. Numerous clinical trials have demonstrated tDCS to be a safe and tolerable device without any major adverse events (Fregni et al., 2005; Fregni et al., 2006; Hummel et al., 2005; Kantak et al., 2010). Studies from our lab have also shown tDCS to have minimal or no adverse effects (Devanathan & Madhavan, 2016; Madhavan & Stinear, 2010; Madhavan, Weber II, & Stinear, 2011; Sriraman, Oishi, & Madhavan, 2014). A recent review concluded that human studies that evaluate the parameters of neuronal damage, such as neuron specific enolase (NSE), electroencephalography (EEG) and neurophysiological tests support the safety of tDCS (Antal et al., 2017; Iyer et al., 2005; M. A. Nitsche et al., 2003) Tadini et al. 2011). Typically, tDCS related dosage parameters include a current intensity of 0.5 – 2 mA with most stimulation electrode sizes of 5 x 7 cm. This electrode configuration creates a net current density of approximately 0.029 mA/cm^2 when currents are applied for 20 minutes. M. A. Nitsche et al. (2003) reviewed tDCS induced adverse events from studies that included approximately 500 healthy subjects from 2000 to 2003 with dosage parameters as mentioned above. The major common adverse events (AE) reported were mild tingling sensations that occurred under the electrodes during stimulation. Another study (Poreisz, Boros, Antal, & Paulus, 2007) examined the adverse events (AE) from 567 tDCS sessions that were administered to healthy volunteers and patients with migraine, stroke and tinnitus. The most common AEs were mild tingling sensation (70.6 %), moderate fatigue (35.3 %), slight itching under the stimulating electrode (30.4 %), headache (11.8 %), nausea (2.9 %) and insomnia (0.98%) (Poreisz et al., 2007) (Please refer to Table 1). Transient redness and contact dermatitis following tDCS has also been reported in a few studies (Riedel, Kabisch, Ragert, & von Kriegstein, 2012). Contributing factors to these AEs include electrode position, pre-existing conditions such as skin allergies, high skin-electrode impedance (dry electrode, solution salinity of electrode sponges, incorrect electrode fixation), prolonged duration, high current density (high current, small electrode) (Dundas, Thickbroom, & Mastaglia, 2007; McFadden, Borckardt, George, & Beam, 2011; Palm et al., 2014) The occurrence of AEs can be prevented by careful adherence to protocol and necessary precautions (such as screening for hypersensitivity and monitoring). Skin irritation can be prevented by adequate preparation of the skin and stimulating electrode. Several studies have also evaluated possible AEs of tDCS in perceptual and cognitive domains by testing performance on neurocognitive tests following tDCS. tDCS does not appear to cause apparent perceptual or cognitive AEs in healthy subjects (Iyer et al., 2005).

To summarize, when adhering to standard stimulation parameters (1 – 2 mA) and 15 – 20 min duration, single and repeated sessions of tDCS show benign study effects such as mild to moderate, tingling or itching and/or a burning but not painful sensation that do not outlast the stimulation period. Although headache, fatigue and light headedness may also be occasionally reported, they are typically transient and rarely require medical management.

Remotely Supervised tDCS as an intervention in ALS

Need for remotely delivered tDCS: Several clinical trials have shown that multiple tDCS sessions are required to produce greater benefits in clinical outcomes, especially in clients with limited motor recovery, where tDCS related effects are thought be cumulative (Acler et al., 2013; Ferrucci et al., 2014; Meesen, Thijs, Leenus, & Cuypers, 2014; Mori et al., 2010; Mori et al., 2013; Rosso et al., 2014). Most tDCS based studies thus far have been conducted in a laboratory-based setting. There are several barriers for accessing tDCS based studies. Repeated tDCS application requires participants to travel to the lab for each treatment session, which can be burdensome to patients and their caregivers. Especially because the tDCS sessions last only for 20 minutes and the participants have to spend anywhere between 2-3 hours to travel for this session (Brunoni, Ferrucci, et al., 2012; Brunoni, Nitsche, et al., 2012; Ferrucci et al., 2014; Holland & Crinion, 2012; Meesen et al., 2014; Vaseghi, Zoghi, & Jaberzadeh, 2014). Some studies have reported significant drop-out rates when participants were treated with tDCS sessions that were administered over 6 months (Loo et al., 2012; Martin et al., 2013). Moreover, when the target population has a progressive neurological disorder such as ALS, there is a higher drop out as reported in several intervention-based studies (Bello-Haas et al., 2007; Sanjak, Bravver, Bockenek, Norton, & Brooks, 2010). Patients receiving palliative care often rely on their caregiver and may not comply with traditional research protocols. This causes ineffective data collection and underpowered tDCS studies which reduce the generalizability of this promising device.

tDCS suitability for remote supervision: A possible solution to ameliorate the feasibility problem is remotely supervised self-administration of tDCS, with a protocol that is safe, well-tolerated, easy to administer and reproducible. A recent study (L. E. Charvet et al., 2015) provided recommendations for staff and end user training, assessment of the participant's capability for self-administration of tDCS, and guidelines to formulate device usage and training manuals. Of particular importance in their recommendations, is a specially designed tDCS equipment that carefully regulates use by the patient. In addition, extensive training procedures that include safety checks at each step that are remotely monitored by study staff can guide safe and reproducible tDCS application. Study 'stop' criteria are also provided that need to be reviewed at several time-points (screening, baseline, study sessions and follow-up visit) during the course of the study for each subject. The subjects need to be initially trained by research staff to monitor their aptitude and tolerability to stimulation.
L. E. Charvet et al. (2015) also emphasize strict dose control for each session. The device suggested is a pre-programmed tDCS device that is dependent on a code for activation for a single session (where the dosage would be pre-determined by the researcher) at a time. After a single use, the device would be inert until a new code is provided. Study staff would provide the unlock code, once safety and tolerability checks have been established, including correct placement of the device, headset and electrodes via a teleconferencing platform. Finally, research staff need to be trained for preparation and testing of the device and its accessories (electrodes) prior to release to subjects and adequate documentation. Training will also include remote monitoring of subjects for any unexpected adverse events (discomfort experienced with the device) or misuse of the device. At the end of the study, staff would also be trained on evaluating the device materials and downloading the stored data from the device. Adverse effects will be monitored, and subjects would be required to report any atypical pain/discomfort during/after stimulation. If the adverse effects cross the study stop criteria, the session should be stopped in

order to prevent further risks and research staff will assess if the AE has occurred due to device factors (improper electrode placement) or subject factors (low threshold for pain).

The authors conclude that remotely supervised tDCS could be incorporated as an extension to tDCS administered in a clinical setting. Careful consideration of staff training, user aptitude and compliance need to be ensured to maintain the same level of safety and tolerability that is typically experienced in a lab/clinic-based setting. Other study protocols following these guidelines are currently ongoing for exploring the effectiveness of home based tDCS in patients with Multiple Sclerosis (Kasschau et al., 2016; O'Neill, Sacco, & Nurmikko, 2015). In a pilot study on MS, Kasschau et al. (2016) proposed 10 remotely supervised tDCS sessions over 2 weeks. The first two sessions of the study were in-person training sessions and the remaining eight were remotely supervised. In the second session, study personnel went to the participant's home to determine appropriate device setup and environmental suitability. Thus far, 20 participants have completed a total of 192 sessions without any adverse event or discontinuation of treatment. All remotely supervised sessions (n = 152) were executed successfully with optimal electrode placement, device operation and adequate tolerability to stimulation. By including comprehensive training and ongoing supervision of participants, the study has achieved high compliance and tolerability. As portable tDCS devices have become available, patients/caregivers can be easily trained in its application and patients may safely use the device at home without the need for regular visits to the laboratory. These authors discuss the use of specially designed devices for supervised tDCS with instruction manuals, and real time monitoring through video conferencing platforms. Taken together, these studies emphasize the feasibility for remotely supervised tDCS devices for patients with progressive neurological disorders (such as ALS, MS) who cannot frequently commute to a lab-based setting because of their impairments.

3.0 Objectives/Aims

The purposes of this pilot study are:

1. To determine the safety and feasibility of long-term treatment with remotely supervised anodal tDCS (RS-tDCS) in individuals diagnosed with ALS. We will evaluate safety and feasibility via the occurrence of adverse events and participant dropout rate. Secondary outcomes will include corticospinal excitability measures, walking function and other clinical measures of balance, gait and strength which will be described subsequently.
2. To determine the effects of 24-weeks of RS-tDCS on disease progression in individuals with ALS. Subjects will be randomized into one of two groups: remotely supervised tDCS or delayed-start control group. The intervention group will receive 24 weeks of anodal tDCS (3 times/week; 72 sessions). The delayed-start group will first receive sham tDCS for 12 weeks followed by a switch to anodal tDCS for 12 weeks. Secondary outcomes will include the ALS Functional Rating Scale (Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.

3. To determine the effects of RS-tDCS on upper (UMN) and lower motor neuron (LMN) mechanisms in individuals with ALS, quantified using Upper and lower motor neuron mechanisms will be assessed using single-pulse transcranial magnetic stimulation (TMS). Subjects will be randomized into one of two groups: remotely supervised tDCS or delayed-start control group. The intervention group will receive 24 weeks of anodal tDCS (3

times/week; 72 sessions). The delayed-start group will first receive sham tDCS for 12 weeks followed by a switch to anodal tDCS for 12 weeks. Secondary outcomes will include corticospinal excitability measures which will be described subsequently.

4.0 Eligibility

4.1 Inclusion Criteria

The general inclusion criteria will be approximately 100 males and females of any race or ethnic status with the following characteristics:

- Age between 18 – 80 years
- Diagnosis of possible, probable, or definite amyotrophic lateral sclerosis according to El Escorial revised criteria
- Spinal onset ALS with initial weakness in the upper or lower extremity.
- Diagnosed with ALS within the past 5 years
- 1-2 point change in pre-slope of the ALSFRS-R at time of enrollment (ratio of drop in score from 48 to the duration in months from onset of weakness)
- Score ≥ 2 for "swallowing" of the ALSFRS-R
- Score ≥ 2 for "walking" of the ALSFRS-R
- Able to provide informed consent
- Stable dose of riluzole, edaravone, AMX0035 (Relyvrio) or no medications
- Availability of a caregiver for remote administration of tDCS

4.2 Exclusion Criteria

Our general exclusion criteria for all subjects will include:

- Subject has bulbar onset ALS
- Any neurological diagnosis other than ALS
- Psychiatric disorders
- Any other concomitant disease that affects prognosis of ALS inclusive of systemic disease, cardiovascular disease, hepatic or renal disorder
- Tracheostomal or noninvasive ventilation for more than 12 hours per day
- Enrollment in an on-going ALS pharmaceutical trial
- Subject plans on moving within 6 months.

As necessitated by the risks of TMS, the exclusion criteria for all subjects will include 1) implanted cardiac pacemaker, 2) metal implants in the head or face, 3) unexplained, recurring headaches, 4) history of seizures or epilepsy, 5) currently under medication that could increase motor excitability and lower seizure threshold: antidepressants such as maprotiline and clomipramine, and antipsychotics such as chlorpromazine and clozapine (Pisani, Oteri, Costa, Di Raimondo, & Di Perri, 2002), 6) skull abnormalities or fractures, 7) concussion within the past six months, and 8) currently pregnant:

Other than the TMS exclusion criteria, tDCS exclusion criteria will also include

- Extreme skin hypersensitivity
- History of contact dermatitis
- History of allodynia and/or hyperalgesia
- Any other skin/scalp condition that could potentially be aggravated by tDCS

Participant eligibility will be confirmed upon completion TMS and tDCS safety questionnaire on the phone as well as on the day of screening. Females of childbearing age will be screened with an instant urine pregnancy test that the lab will provide to confirm negative pregnancy. Subjects would be required to inform the research personnel immediately if they are pregnant after beginning the study. If subjects become pregnant during the study, we will exclude them from participating in the study and ask them to surrender their tDCS device. Subjects will not be excluded if they do not have access to videoconferencing capabilities. Instead, tablets with prepaid data will be provided to these participants.

4.3 Excluded or Vulnerable Populations: N/A

5.0 Subject Enrollment

Individuals with ALS will be recruited through the use of an email script (Supplement_E-mail Announcement) and flyer (Supplement_Flyer ALS RStDCS) which will be posted at UIC, University of Chicago as well as via the web (UIC Announcements, UIC-AHS labs webpage, UIC Massmail, ALS Association support groups and outpatient clinics). Individuals will also be recruited through online postings on a College of Applied Health Sciences subject recruitment page (https://ahs.uic.edu/research/participate-in-research/) and on our lab webpage (https://bpl.ahs.uic.edu/participate/). Text to be displayed on these webpages is shown in the supplemental document (Supplement_Online Study Recruitment Text). The flyer (Supplement_Flyer ALS RStDCS) and email script (Supplement_E-mail Announcement) will provide contact information for interested individuals to directly contact a member of the research team. Research personnel will explain the study and answer all questions. If the individual is interested, they will be screened over the phone. If the individual is eligible, they will be scheduled for a visit to the research sight.

Furthermore, individuals with ALS will also be recruited by physician referral from the Department of Neurology at UIC and the University of Chicago. Physicians will inform eligible patients about the study during their routine visits to the clinic, and if the patient seems interested physicians will provide a flyer (Supplement_Flyer ALS RStDCS) containing the Brain Plasticity Lab contact information. To minimize potential coercion, co-investigators will not be involved in obtaining informed consent from the patients. It will be made clear that the study is solely being conducted for research purposes and will in no way provide treatment for their symptoms. If the patient is interested in knowing more about the study, the patient will initiate contact with key research personnel. Screening and informed consent will be conducted by key research personnel only and not by the referring physician (to avoid possible coercion by the treating neurologist who may be the patient's primary care physician).

Patients who have been previously seen in the ALS clinic will be contacted by mail and/or telephone. A letter informing patients about the research will be sent by the ALS clinic. Dr. Abrams and/or his staff members will also contact previous patients by phone to ascertain if patients have an interest to be contacted by the research team to participate in the study. If a patient expresses an interest to participate in research, their name and contact information will be provided to the research team for future contact.

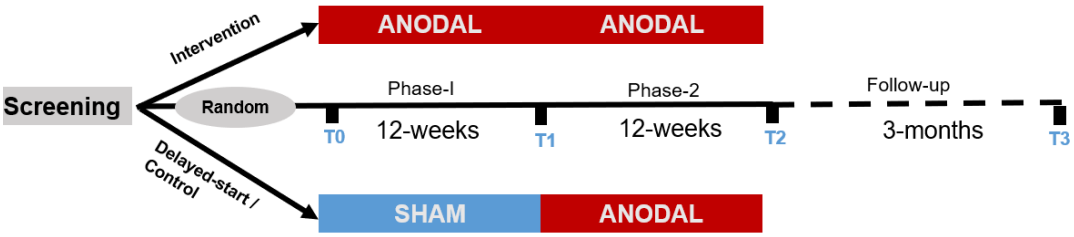
To aid recruitment, we will also use the UI Health EPIC electronic health record system. Specifically, we will use EPIC to identify potential participants who have been diagnosed with ALS and have been treated at UI Health. Individuals who have ALS and meet other study inclusion criteria will be contacted first with one email (Supplement_E-mail Announcement). After 7 days, if the research team has not received a response to the email, we may contact the individual with one phone call (attached phone script). No additional attempts will be made to contact potential participants if no response is received to the email or phone call. If a response is received from the individual indicating interest in the study, they will undergo screening procedures.

6.0 Study Design and Procedures

General Overview

Subjects will attend 1 tDCS tolerability test and training visit, 7-10 testing sessions (2-3 at T0, 2-3 at T1, 2-3 at T2, and 1 follow-up at T3) and 72 remotely supervised tDCS sessions. Testing sessions at four timepoints will involve two to three visits (depending on availability and capacity of the participant). Visit 1: obtain informed consent and administer a pregnancy test, complete the Medical Screening Questionnaire and the TMS and tDCS Safety Questionnaire, measure blood pressure, and perform clinical assessments (1-2 hours). Visit 2: Upper and lower motor neuron mechanisms will be assessed using single-pulse transcranial magnetic stimulation (TMS).

Visit 3: tDCS tolerability testing (30 minutes) will be performed and subjects will be asked to return to the lab with their caregivers for a training session on the use of the Soterix tDCS Mini-CT device (1.5 - 2 hours.). The visits maybe combined if the patient wishes to reduce their travel time. Remotely supervised tDCS sessions are expected to last for 45 minutes which will include up to 20 minutes of stimulation with RS-tDCS and an additional 25 minutes for setting up video conferencing and RS-tDCS equipment. The follow-up testing session will be combined into one visit (up to 4 hours) consisting of the same outcome measures recorded at T0, T1, and T2. If subjects are in the delayed start group, they will receive 24 sessions of sham stimulation followed by 24 sessions of anodal tDCS.



Study Design: Participants will be randomized to receive either sham RS-tDCS (delayed-start control) or facilitatory anodal RS-tDCS (intervention). The intervention group will receive 24 weeks of anodal tDCS (3 times/week; 72 sessions). The delayed-start group will first receive sham tDCS for 12 weeks followed by a switch to anodal tDCS for 12 weeks. Outcome measures will be administered at four time points at entry (T0), at the end of 12 weeks (T1), at the end of 24 weeks (T2) and at a 3-month follow up (T3).

Randomization: Stratified treatment assignment of participants into the two groups will be based on baseline ALFSRS-R score and the pre-slope. Group assignment will be randomized within each category using sequential randomization to achieve study arm balance. Participants and assessors will be masked to the type of stimulation they receive.

Remotely Supervised tDCS as an intervention in ALS

Safety: Participants will make two interim visits to the lab after every 6 weeks for a safety check (scalp integrity and Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.
The number of adverse events (AE) will be actively monitored using structured questionnaires that enquire for AEs related to tDCS during training and lab visits. Key AEs of interest will include 12 symptoms including clinical seizures, skin injury and neurological deterioration. The safety of each participant will be assessed on an individual basis throughout his or her involvement with the study.
Feasibility: Recruitment and randomization will be assessed using frequency approached for screening and enrollment. Retention will be assessed using proportion of participants enrolled after screening eligibility and number who completed the study. Acceptability of treatment will be examined using semi-structured patient, caregiver and clinician feedback questionnaires regarding perceived satisfaction, perceived ease-of-use, strengths and weaknesses (Supplement_Final Survey Questions). All participants will be required to complete feedback questionnaires. These questionnaires will contain close-ended questions which use a Likert scale and open-ended questions on treatment perception and attitudes. Adherence will be measured by rate of patient dropouts. Tolerability will be measured by pleasant/unpleasant ratings using a visual analog scale for each session.
All subjects will continue with their standard-of-care treatment while participating in the research.

Screening and clinical examination testing visit
Subjects will report to the Brain Plasticity Lab at UIC located at 1919 W. Taylor St, #810, Chicago, IL 60612. All subjects will sign a written informed consent. Females of childbearing age will undergo a urine pregnancy test. Subjects who test positive will not be eligible to participate. Female participants of childbearing age will also be informed that the effects of tDCS on pregnancy are still unknown. If participants of childbearing age are planning to get pregnant or may be pregnant during the 24-week period, they will be instructed to stop the tDCS immediately and will be excluded from the study. All subjects will be asked to complete a medical screening questionnaire and TMS and tDCS safety questionnaires. The medical screening questionnaire will include questions about age, gender, race, medical history, medications and personal habits (such as smoking). The TMS and tDCS safety questionnaire will include questions pertaining to the TMS and tDCS exclusion criteria. Blood pressure will be measured prior to conducting clinical assessments. The first testing visit will last for 1 – 2 hours.

Clinical assessments

Clinical testing will take approximately 60 minutes to complete. The battery of functional measures are listed below, and will include tests of walking and balance. The tests have been validated and are commonly used, non-invasive clinical measures.

- Revised ALS Functional Rating Scale (Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.
  91. This will be conducted every two weeks over the phone or Zoom PHI.
- Gait speed will be measured using the average speed over two trials of the 10MWT.
  Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from

0 to 48, with higher scores indicating more function retained.
Self-selected and fast walking will be measured as the average walking speed from 2 trials of the 10-m walk test, a reliable and sensitive marker for function in patients with ALS.

- 10-meter walk: The 10-meter walk test (10MWT) is a performance measure used to assess walking speed in meters per second over a short distance. It can be employed to determine functional mobility, gait and vestibular function. We will also employ the use of APDM wearable sensors during the test to assess outcome measures of functional mobility.
- Ankle motor control will be assessed using a sinusoidal tracking task.
  A custom-built ankle-tracking device will be used to quantify the participant's ability to track a computer-generated sinusoidal target with ankle movement
- Other measures: We will examine patient perspective on health outcomes using the Health Related Quality of Life scale, EuroQual-Visual Analog Scale and fatigue using the Fatigue Severity Scale (FSS), 9-item measure from 1 to 7, higher scores = more severe fatigue.

Safety and Feasibility: The number of adverse events (AE) will be actively monitored using structured questionnaires that enquire for AEs related to tDCS during training and lab visits. Key AEs of interest will include 12 symptoms including clinical seizures, skin injury and neurological deterioration (tDCS adverse event questionnaire). The safety of each participant will be assessed on an individual basis throughout his or her involvement with the study. Recruitment and randomization will be assessed using frequency approached for screening and enrollment. Retention will be assessed using proportion of participants enrolled after screening eligibility and number who completed the study. We will collect reasons for study refusals and withdrawals. Acceptability of treatment will be examined using semi-structured patient, caregiver and clinician feedback questionnaires regarding perceived satisfaction, perceived ease-of-use, strengths and weaknesses

Transcranial magnetic stimulation (TMS) and peripheral nerve stimulation (PNS) testing visit

TMS procedures
The TMS procedure will be conducted in the UIC Brain Plasticity Lab. This is the same TMS procedure that has been successfully used in our other research studies (e.g., IRB #2015-0764, #2011-0676, # 2015-1127, # 2011-0284). TMS is a safe, non-invasive method of brain stimulation that has been widely used to study the physiology of the representations of muscles in the motor cortex in healthy and neurologically disordered individuals (Anand & Hotson, 2002). Very short duration (< 1 ms) magnetic pulses are applied via an insulated wire coil placed on the intact scalp overlaying the motor cortical area projecting to a target muscle. Each pulse induces a motor evoked potential (MEP) in a target muscle that can be readily monitored by recording EMG from that muscle. A figure-of-eight or double cone coil is typically used to deliver focal magnetic pulses to a number of scalp sites over the cortical area representing a muscle of interest. Self-adhesive disposable electrodes (Suretrace) with an inter-electrode distance of 2 cm will be applied over the muscle bellies of the tibialis anterior (TA) in the lower

extremity. A ground electrode will be applied over a proximal bony prominence. Standard skin preparation techniques (light abrasion and cleansing with alcohol) will be completed prior to application of the electrodes. EMG recordings will be amplified (Delsys Bagnoli system), band-pass filtered (10-1000 Hz), and sampled at 5000 Hz.

Subjects will be seated, and magnetic stimuli will be delivered via a figure of eight or double cone coils connected to a Magstim 200 unit (Magstim Company, Boston MA). Resting motor threshold for the muscle of interest will be defined as the stimulator output intensity that can elicit a MEP with peak-to-peak amplitude of at least 0.075 mV in four out of eight trials. It will be determined by increasing stimulus intensity in steps of 1% stimulator output. Active thresholds will be determined with the same protocol and defined by the lowest stimulus intensity required to elicit a MEP with a peak-to-peak amplitude of at least 0.1 mV in four out of eight trials with the subject contracting the muscle of interest to about 10% of maximum voluntary contraction. TMS measurements will involve generating MEPs for each muscle. Short intracortical inhibition (SICI) was measured at an interstimulus interval of 2.5 ms. A subthreshold pulse (80% active threshold) was set as the conditioning stimulus and a suprathreshold pulse was set (130% active threshold) as the testing stimulus. To assess corticospinal excitability of the M1, the figure of eight or double cone coil will be placed over the M1 cortical area (near the vertex of the head) and the subject will then receive 15 - 30 stimuli at intensities corresponding to 80% to 130%of rest and active threshold. These measures will assist the investigators to assess the contribution of the motor cortex to the upper and lower limb muscles. The entire procedure should take about 2 hours.

PNS procedures
The PNS procedure will be conducted in the UIC Brain Plasticity Lab under the supervision of Dr. Rezania. Peripheral nerve stimulation (PNS) will be used to assess lower motor neuron integrity.
Very short duration (1ms) electric pulse is applied to the skin overlying the peripheral nerve that projects to a target muscle. Each pulse induces two evoked potentials in a target muscle that can be readily monitored by recording EMG from that muscle. The first evoked potential is the M-wave and the second is referred to as the H-reflex. The M wave arises from direct stimulation of the motor nerve serving the muscle and its amplitude is used as an estimate of the stimulus intensity delivered to the sensory nerve whose excitation generates the H-reflex. The maximum amplitude M wave that can be obtained in an individual is referred to as the M max, and the stimulus intensities used expressed as a percentage of that needed to produce M max.

Stimulating electrodes will be placed on the lower limb on the skin over the fibular head, longitudinal to the estimated path of the common peroneal or tibial nerve. For upper limb stimulation, stimulating electrodes will be placed on the skin 2cm above the elbow on the lateral part of arm, longitudinal to the estimated path of the radial nerve or on the skin above the wrist joint, longitudinal to the estimated path of the ulnar nerve.

Peripheral nerve stimulation (PNS) will be used to assess lower motor neuron integrity.
Similar to TMS, Peripheral nerve stimulation (PNS) will be used to assess lower motor neuron

integrity.
The resting and active threshold for eliciting H-reflexes will be determined for each muscle.

H-reflexes will be evoked using a 1-ms square wave pulse, via a Cadwell Sierra Summit EMG/NCV/EP machine (Cadwell Laboratories, Inc., Kennewick, WA). As outlined in the TMS procedure above, resting motor threshold for the muscle of interest will be defined as the stimulator output intensity that can elicit H-reflex waveforms with peak-to-peak amplitude of more than 50 μV in four out of eight trials. Active thresholds will be determined with the same protocol, however with the subject contracting the muscle of interest to about 10% of maximum voluntary contraction. The magnitude of the M wave, which arises from direct stimulation of the motoneuron axons serving the autogenic muscle, will be used as an estimate of the stimulus intensity delivered to the large diameter afferent fibers.

The subjects will receive 6 stimulations at each of 7 intensities ranging from 70% of H-reflex active threshold to 110% M max.

Pairing the magnetic and peripheral nerve stimuli allows investigators to assess the cortical contributions to spinal mechanisms underlying changes in the H-reflex. TMS delivered at intensities below motor threshold will be specifically timed to arrive at the spinal cord just before the afferent volley from Peripheral nerve stimulation (PNS) will be used to assess lower motor neuron integrity.
This is called a TMS conditioned H-reflex. TMS conditioned H-reflex recruitment curves will be elicited, using the same Peripheral nerve stimulation (PNS) will be used to assess lower motor neuron integrity.
Six paired stimuli will be delivered at each of 7 intensities ranging from 70% of H-reflex active threshold to 110% M max.

tDCS procedures
tDCS is a safe and painless technique to increase or decrease motor system excitability. This involves the application of weak electrical currents to the scalp and has been widely used to improve motor function in neurologically disordered individuals without any adverse effects (30). 2mA Anodal tDCS (anodal electrode over the motor cortex and cathode over the contralateral orbit) enhances cortical excitability, which increases the amplitude of motor evoked potentials. Saline soaked sponge electrodes will be attached over the scalp to the target area and to the skin above the contralateral orbit. Transcranial current will be induced using a Soterix Medical 1X1 tDCS mini-CT Stimulator (Soterix Inc., New York, New York, USA). Current will be increased slowly over a 30 second period which will help the subjects get accustomed to the tingling sensation associated with the current.

Remotely Supervised tDCS sessions
Remotely supervised tDCS sessions will take place at the participant's home three times a week for 24 weeks for a total of 72 sessions. These sessions are expected to last for 45 minutes which will include up to 20 minutes of stimulation with tDCS and an additional 25 minutes for setting up video conferencing and RS-tDCS equipment. The sham stimulation will be programmed into the device for those in the delayed start group. Previous studies have shown that participants

typically do not know the difference between sham and real stimulation, enabling the study to remain blinded.

tDCS tolerability test and training visit
All subjects will report to the lab for a tDCS tolerability test. Lab personnel will test the subject's tolerability to stimulation with tDCS. tDCS electrodes will be placed on the subject's scalp and stimulation will be performed for 20 minutes. Subjects will be assessed for side effects. Subjects will also complete a RS-tDCS training session which will last for 1.5 – 2 hours.

Device information and training of study personnel
A portable tDCS device (Soterix Medical 1X1 tDCS mini-CT Stimulator) will be issued to the subject upon completion of training. All subjects will be directly trained by research personnel. Research personnel will be trained by the device manufacturer (Soterix Inc.) in the preparation and testing of the tDCS device and electrodes prior to providing it to participants, as well as appropriate documentation of the device release. This device has built in programmable codes which allows for strict dosage control which can be monitored remotely. The device would be deactivated until a code is provided by the research staff to the subject for every session. The code unlocks a single session with a pre-set duration and intensity that would be pre-programmed. After a single discharge, the device is inert until a new code is provided. This allows the remote supervisor to control tDCS application, as the code may not be provided until the researcher is satisfied with the placement of the electrodes via video conference. The subject or caregiver cannot change stimulation intensity or treatment duration which enhances safety and reproducibility.

Study staff will be familiarized on the usage of the device and the location of headset placement. In addition, selected research staff (who are not blinded to the study) will be trained with and have access to the device manual that enlists in a step-by-step fashion, the procedures that are required to program the device prior to release to subjects, for example programming device unlock codes for one-time use to be provided prior to each session. Prior to releasing a device to a subject, study staff will program the intensity, duration, and condition of each planned session, along with a code that limits the number and frequency of sessions. This will be double checked by the Principal Investigator prior to release of the device to the subject. Through the duration of the study, study staff will be trained to monitor subjects for any unexpected adverse events (e.g., atypical discomfort) or misuse of the device. At the end of the study, study staff will evaluate retrieved device materials (e.g., headgear/stimulator condition, gel) and download any data stored on the device (e.g. completion codes for each subject's study sessions, stimulation history of each code issued) as relevant to confirm compliance.

<u>Training of subject/ caregiver:</u>
At the training visit, study personnel will complete a tDCS checklist (Supplement _tDCS checklist) to screen subjects for at home RS-tDCS. In the training session, the participant and caregiver will be familiarized to the device, electrode positioning and placement on the scalp. The subject/caregiver will be trained to properly apply the headset and correctly operate the device.
At the training visit, subjects will be measured for individually fitted and engineered headband locators for electrode placement. Headbands are measured and marked relative to ear tragi, the

nose and midline of scalp. A separate occipital band ensures the locator headband cannot slip from its position. The headgear will allow consistent placement of electrode at the lower limb motor cortex area on the scalp (1 cm posterior and 1 cm lateral to the vertex, Cz). The headgear will be marked with "RED" and "BLACK" to confirm that color coded leads are properly placed, ensuring Anode (Red) and Cathode (Black) and the subject is shown how the electrodes are placed (see figure). Once fitted, subjects are shown how to position the headbands reproducibly and instructed on how to position the band markers relative to the anatomical landmarks described. The subject/caregiver will then demonstrate tDCS application and electrode placement under the supervision of the researcher. The research personnel will use a checklist to identify if the participant/caregiver has understood device operating instructions.

Photographs and measurements will be taken in case the subject needs for reference at home and all instructions are given in an information guide as well. The investigators will then confirm that the subject and caregiver /partner have understood all details of the stimulation. We will provide study training materials i.e. an information guide (Supplement_Information guide and Stimulation Manual), a RS-tDCS session log [to record the number of treatment sessions] (Supplement_tDCS session log), and RS-tDCS equipment (headgear and 12 electrode sets) along with other supplies for the entire study. We will also provide a RS-tDCS side effects survey (Supplement_tDCS side effects survey) in which subjects are informed of potential side effects such as tingling, burning sensation, dizziness, headache, nausea and phosphenes while switching the device on or off abruptly. Subjects will also be provided a RS-tDCS ease of use form (Supplement_tDCS ease of use) for reporting their experience of equipment use, including convenience.

Following the training visit, the subject would be provided a schedule for RS-tDCS sessions (monitored via Zoom PHI). The researcher will remotely observe the placement of the electrodes and the headset and supervise each of the 72 sessions. The subject will also be asked to report adverse effects at the beginning and end of every session. Participants will be instructed to contact the Emergency Department in the event of experiencing serious side effects.

Study stop criteria (Supplement_study stop checklist) will be reviewed at each stage of the study: baseline, study sessions and post study completion. Throughout the study, we will monitor compliance via the stop criteria to exclude participants who fail to set up the device properly. We will monitor each session and dosage of current using codes. If any participant reports discomfort, pain or a desire to withdraw, their participation may be terminated. The session log will be reviewed by the study staff every 2 weeks until the end of the study.

Study stop criteria (adapted from Charvet et al. 2015)

- Does not pass tDCS aptitude test
- Does not tolerate tDCS
- Three reschedules/ failures to initiate video conferencing
- Failure to place headset correctly within 15 minutes at more than one session

- Subject experiences any severe adverse event such as an event resulting in death, life-threatening event, initial or prolonged hospitalization, disability or permanent damage, or event requiring intervention to prevent permanent impairment or damage

In addition, a pre-specified interim analysis for the continuation of the entire study will be completed after the first 6 participants complete the study. The adverse events and mean change in Change in Revised ALS Functioning Rating Scale (ALSFRS-R). Scores range from 0 to 48, with higher scores indicating more function retained.
The stopping criteria will be defined as a mean difference between groups exceeding 2 standard deviations. If this occurs, the study will be stopped for full review by the medical monitor or revising the protocol before proceeding.

7.0 Expected Risks/Benefits

7.1 Risks

Risks associated with the TMS procedure:
1) Seizures: Rare cases have reported the development of seizures during or immediately after magnetic brain stimulation. Individuals who have a history of seizures or have been diagnosed with epilepsy will be excluded from this research study (by thoroughly screening subjects we hope to minimize this risk). Single pulse TMS that we use in this study has been deemed to carry little risk beyond occasionally causing local discomfort. Our stimulation procedures follow published safety guidelines. Seizure activation is extremely unlikely with the single pulse low numbers of stimulation proposed in the current investigation.
2) Discomfort: A small number of people find TMS uncomfortable, particularly at high intensities of stimulation. If individuals report feelings of discomfort, stimulation intensity will be reduced or, if not feasible, testing will be terminated.
3) Muscle Twitching: Subjects may feel twitches in the muscles of the arm, leg or face during the magnetic stimulation.
4) Noise: A loud click during magnetic stimulation may be heard. Subjects will be provided with foam earplugs that can effectively prevent this discomfort.
5) Skin Irritation: There is a risk of mild skin irritation at the location where the electrode sensors have been placed, but this usually consists of minor redness that will go away quickly after they are removed.

Risks associated with clinical assessments and balance testing:
1) There is a possibility that subjects may lose balance while getting up from sitting or walking or performing the balance test. An authorized research personnel will be present at all times to ensure safety of the subject. A gait belt will be used when the subjects are performing the clinical tests and a safety harness will be used when necessary for balance testing.
2) Muscle Soreness or Fatigue: During or following testing subjects may feel temporary muscle aching or general fatigue. Individuals with ALS who are in the treatment group may feel muscle soreness or fatigue associated with training. Risks of both muscle soreness and muscle fatigue will be minimized by terminating training if greater than moderate muscle soreness occurs.

Risks associated with RS-tDCS:

1) Discomfort: Subjects may feel tingling or itching when tDCS is being delivered or at the spot where the electrodes are placed. This usually goes away in a minute or so. In a low percentage of people, there is a side effect of nausea or insomnia. If subjects report any symptoms that make the stimulation not tolerable, they can be excused from participating at any time.
2) Pain: Participants will be provided a list of standard safety precautions to minimize any risk of harm to themselves or damaging the device. The participants will be informed of typical tDCS side effects such as tingling or itching, which should never be painful. If they feel any pain concentration in one area, they would be asked to abort the stimulation, remove the headband and check the skin for any redness or discoloration. Study personnel would then evaluate if treatment can be continued.
3) Light headedness/ phosphene flash: tDCS will automatically stop if the electrode-skin contact is poor. The current intensity will drop to zero, and it is possible that the participant may feel transient light headedness or even see a phosphene flash. Although these symptoms are unusual, they must inform the study personnel so that they can investigate the cause of poor electrode contact.
4) Skin redness/burns: The participants will also be instructed not to administer tDCS over skin that is damaged including any cuts, scratches or scars as this could lead to current concentration in that area, causing skin burns. In the event of an accidental application, the participant must notify the study personnel immediately.
5) Remaining still: Subjects will need to remain still during the tDCS procedure. The tDCS device must be kept on a flat, secure surface during the stimulation procedure. Subjects will need to avoid any head movements that could jerk the cables or cause the tDCS device to fall on the floor and potentially disconnect the electrodes.
6) Worsening of pre-existing medical condition: If the participant notes a worsening of a pre-existing medical condition, such as migraines or balance because of treatment with tDCS, the team must be notified immediately. Although the exact safety plan may be specific to the subject's underlying medical condition, information regarding an emergency contact number and contact details for the nearest clinic/hospital will be provided.
7) Feeling anxious: Subjects will be responsible for administering the tDCS procedure themselves so they may feel a little nervous or anxious.
8) Device malfunction: tDCS is a low risk procedure and is not expected to cause serious adverse events. To avoid undue risk of tDCS being delivered at a higher intensity, codes will be used to monitor dosage. It is possible that the device may malfunction or have technical issues. In the event of such a problem, subjects will be instructed to switch off the device and inform the research personnel immediately. In addition, as an added safety feature, the device will not work (discharge) unless the electrodes are correctly applied to the scalp and the electrode contact is adequate. The device will prompt subjects to adjust the placement of electrodes, if necessary.

Other Risks:
1) Subjects will feel a squeezing sensation on their arm when the cuff is inflated during the blood pressure measurement.
2) A risk of this research is a loss of privacy or confidentiality. To minimize this risk, subject study data will be stored and coded. Only authorized research personnel will have access the subject master code and all data.
3) Subjects may feel uncomfortable providing personal information in the questionnaires. They will be instructed to skip any questions that they do not wish to answer.

4) Pregnancy testing: Females of childbearing age who test positive during the testing may be surprised or experience distress if they were unaware. If they are not comfortable taking the pregnancy test, they will not be enrolled in the study.

7.2 Benefits
There is no direct benefit to the individual from participating in this research project.

8.0 Data Collection and Management Procedures
The research will be conducted in compliance with state and federal laws, including the Health Insurance Portability and Accountability Act (HIPAA) which require researchers to protect an individual's health information.
Data will be stored and analyzed in the Brain Plasticity Lab located at 810/834, 1919 W. Taylor St. in Chicago. To minimize breach of privacy and confidentiality, subject data will be stored and coded. Members of the research team will process the data and it will be stored on computer disks on which the subject's data will be referred to by a participant number that will be assigned based on the date of his/her participation. This will ensure that anyone who views the data will not have access to the subject's personal information. The key to the code, which links the subject's participant number to his/her identity will be stored separate from the data and destroyed ten years after study completion.
The Principal Investigator and the research coordinator will have access to the device key for release of treatment (activation) codes.
The primary investigator and co-investigators will have access to the raw data. The raw data will not be made available to any other individuals. When requested by the subject, we will share the results of the experiments.

Study information from this study may be reviewed by representatives of the study group at University of Illinois at Chicago, the Institutional Review Board (IRB) at the University of Illinois at Chicago, and perhaps, the U.S. Food and Drug Administration (FDA). Study records will be kept confidential to the extent provided by the law. The name of individual subjects or other identifying data will not be used in any report or publication of this study.

9.0 Data Analysis

We will look at pre and post changes in our primary and secondary outcomes measures. A one-way ANOVA will be used to examine changes in adverse events, subject dropouts, and TMS and clinical assessments. A two-way repeated measures ANOVA with groups and time as the two factors will be used to analyze change scores on adverse events, TMS and clinical assessments.

10.0 Quality Control and Quality Assurance

We will employ several quality control procedures namely written protocols, training, objective evaluation of tDCS protocols and training research personnel thus maximizing validity and reliability of the protocol delivery and outcome assessments.

As a part of the subject's tDCS kit, a tDCS side effects survey checking for typical side effects that may arise during or after tDCS will be included. Subjects would be instructed to record the presence/absence of each side effect, the severity and duration. Any side effect that is rated very

severe and atypical of tDCS, regardless of whether the subject attributes to tDCS or not, should be reported and assessed by study personnel before further treatment is continued. Guidelines provided to participants can help identify and document adverse events that may be useful in managing any potential risks. In addition, the information guide provided to the subject will minimize any risk of harming themselves or damaging the tDCS device.

To monitor compliance, we will also ensure that participants are familiar with basic functioning of a smart phone/laptop/computer/iPad and how to connect the device to internet via a computer aptitude checklist (Supplement_technical aptitude checklist). We will also ensure that participants have the aptitude to setup the tDCS device. We will choose a secure video conferencing software such as Zoom PHI to allow for remote supervision of the proper setup of the device, optimal electrode-skin contact, and that the intender user is receiving the treatment.

Assessors who are performing the clinical assessments will be blinded to the intervention. Dr. Madhavan will be actively involved with supervising and monitoring the study on a day-to-day basis. She will meet with all study personnel at least once a week to ensure that there is strict adherence to study protocol and outcome assessments. Dr. Madhavan will also hold bi-monthly journal club meetings to ensure that all key personnel are abreast of the scientific literature in the area and the importance of the current research and thereby motivate staff to ensure their best performance during training and assessment. All key research personnel will be provided the adequate training and equipment needed to carry out the study. Training will be repeated as necessary. Dr. Madhavan will check and regularly review any adverse events or deviations from protocol. Study personnel will monitor subject compliance to the protocol and losses to follow up.

11.0 Data and Safety Monitoring

The PI will be primarily responsible for monitoring the safety of participants, and the safety and confidentiality of data. This will be done by following the best practices to ensure that we strictly adhere to the inclusion and exclusion criteria, and protections against risks outlines. The safety of each participant will be assessed on an individual basis throughout his or her involvement with the study, regardless of group assignment. Any decline in function or participant responses that indicates a potential adverse effect will be reviewed individually.
A member of the research team will be available to the subject throughout testing and will be monitoring subject safety throughout. We will ask the subject to provide us with a phone number of a caregiver (or friend or family member) to contact in case of emergency. For the RS-tDCS, the stimulation sessions will be supervised remotely from the research lab using video conferencing. The RS-tDCS device has built in programmable codes which allows for strict dosage control which can be monitored remotely. The device would be deactivated until a code is provided by the research staff to the subject for every session. The code unlocks a single session with a pre-set duration and intensity. After a single discharge, the device is inert until a new code is provided. This allows the remote supervisor to control RS-tDCS application, as the code may not be provided until the researcher is satisfied with the placement of the electrodes via video or phone conference. The subject or caregiver cannot change stimulation intensity or treatment duration which enhances safety and reproducibility. The subject will also be asked to report adverse effects at the beginning and end of every session. The subject cannot operate the

device unless there is another adult present at home in case they are alone and an AE occurs and they are unable to call for help. Participants will be instructed to contact the Emergency Department in the event of experiencing serious side effects.
Before sending the device home, at the training visit, study personnel will complete a tDCS checklist to screen subjects for suitability of RS-tDCS. This will be double checked by the Principal Investigator prior to release of the device to the subject. If the subject qualifies, we will ensure a rigorous training session for the subject and if necessary, the caregiver. We will instruct the subjects to maintain a RS-tDCS log which will be reviewed by staff every 2 weeks until the end of the study. We have many different stops inserted into the protocol for the safety of the participant. The STOP criteria are summarized below:

- tDCS tolerability test – Stop 1: Does not pass tDCS tolerability test, has pain or other adverse effects
- tDCS training visit – Stop 2: Does not understand tDCS
- RS-tDCS sessions:
    - Zoom PHI video call – Stop 3: Three reschedules/ failure to initiate conference
    - Placement of headset: Stop 4: Failure to place headset correctly within 30 minutes at more than one study session
    - Adverse event – Stop 5: Subject reports experiencing any of the critical events
    - Pain- Stop 6: Reporting of a pain score of 7/10 or more at any point
- In addition, a pre-specified interim analysis for the continuation of the entire study will be completed
  after the first 6 participants complete the study. The adverse events and mean change in ALSFRS-R between the 2 groups will then be compared. The stopping criteria will be defined as a mean difference between groups exceeding 2 standard deviations. If this occurs, the study will be stopped for full review by the medical monitor or revising the protocol before proceeding

Dr. Rezania will serve as the medical monitor of the study. A DSMB will be established to monitor the study in terms of timely subject enrollment, integrity of data acquisition and storage, and patient safety. There will be three members who will not be a part of the study team, and who will have no conflicts of interest. The DSMB will include a physician, a scientist with clinical trials experience, and a physical or occupational therapist with experience in working with patients with neurological conditions. Adverse events and unanticipated problems will be reported within 24 hours to the IRB and documented on an Adverse Event Log Sheet in the research records.

12.0 Statistical Considerations

Subjects and their caregivers face difficulties in participating in randomized controlled trials. Some of the issues that limit participation include travel arrangements, travel associated costs, caregiver's time and scheduling of multiple appointments. Hence it is critical to perform a thorough assessment of the potential benefits of RS-tDCS before considering a randomized controlled trial (RCT). We have powered the study to demonstrate safety of RS-tDCS in terms of adverse events. We will study 100 subjects with ALS. For Aim 2, we will be testing 50 subjects per group. For each comparison of 50 subjects with RS-tDCS compared to 50 in the other group, if the true adverse event rates are really equal, we will have 80% power to reject the null of a

higher event rate in the RS-tDCS group. This power will also obtain an estimate of the variance of the treatment effect for use in power calculations for a future study. We have estimated a total of 100 subjects to be included in the study.

13.0 Regulatory Requirements

13.1 Informed Consent

Oral consent will be obtained by phone during the initial telephone screen. Upon determination of eligibility, the initial meeting will take place in Room 810 in the Applied Health Science Building (1919 W Taylor St.) Subjects will meet with Dr. Madhavan and/or key research personnel who will explain the research study. Subjects and/or family will then review the informed consent document and all questions will be answered by the investigator. Informed consent will be obtained in English using lay language. The subject will receive a copy of the signed informed consent document and the investigator will keep the original in the research records. A preparatory to research waiver will be secured by the IRB according to 45 CFR 46 164.512(i)(1)(ii). A waiver of informed consents for the screening, recruiting, and determining eligibility will be secured by the IRB according to 45 CFR 46.116(g).

13.2 Subject Confidentiality

Screening and testing of participants will be conducted in private rooms. Subject's privacy will be protected at all times by ensuring that only key research personnel are present during testing and training. An alphanumeric code will be used to identify each subject. Authorized research personnel will maintain a master sheet which has the subject's name linked to his/her code (initials followed by a number). This sheet will be maintained on the lab computer in a password protected file that only the research team directly working on the project has access to. The other data will be maintained on the lab computers which only authorized personnel have access to. Security of these computers are maintained by the College of Applied Heath Science IT personnel. The key linking the code to the subject's identity will be destroyed 10 years after study completion. Results published will not include names of subjects.

13.3 Unanticipated Problems

Any unexpected experience, adverse events or outcomes related to the research will be closely monitored by the research personnel and reported to Dr. Madhavan immediately. Dr. Madhavan will take necessary action according to the nature of unforeseen problem which will suspension of research procedures in currently enrolled subjects; modification of research procedures for new subjects; changes of the informed consent document/process to ensure subject safety and privacy, modification of inclusion or exclusion criteria to mitigate the newly identified risks; implementation of additional procedures for monitoring subjects; and/or suspension of enrollment of new subjects.