Transcranial Direct Current Stimulation to Treat Aphasia: A Superiority Study

Superiority **T**rial of **A**phasia-focused **R**ehabilitation
with tDCS **S**timulation **(STARS)**

National Clinical Trial (NCT) Identifier: Pending

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Funded by: National Institutes of Health/National Institute on Deafness and Other Communication Disorders (NIH/NIDCD)

Protocol Version Number: 4.0

16 June 2026

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

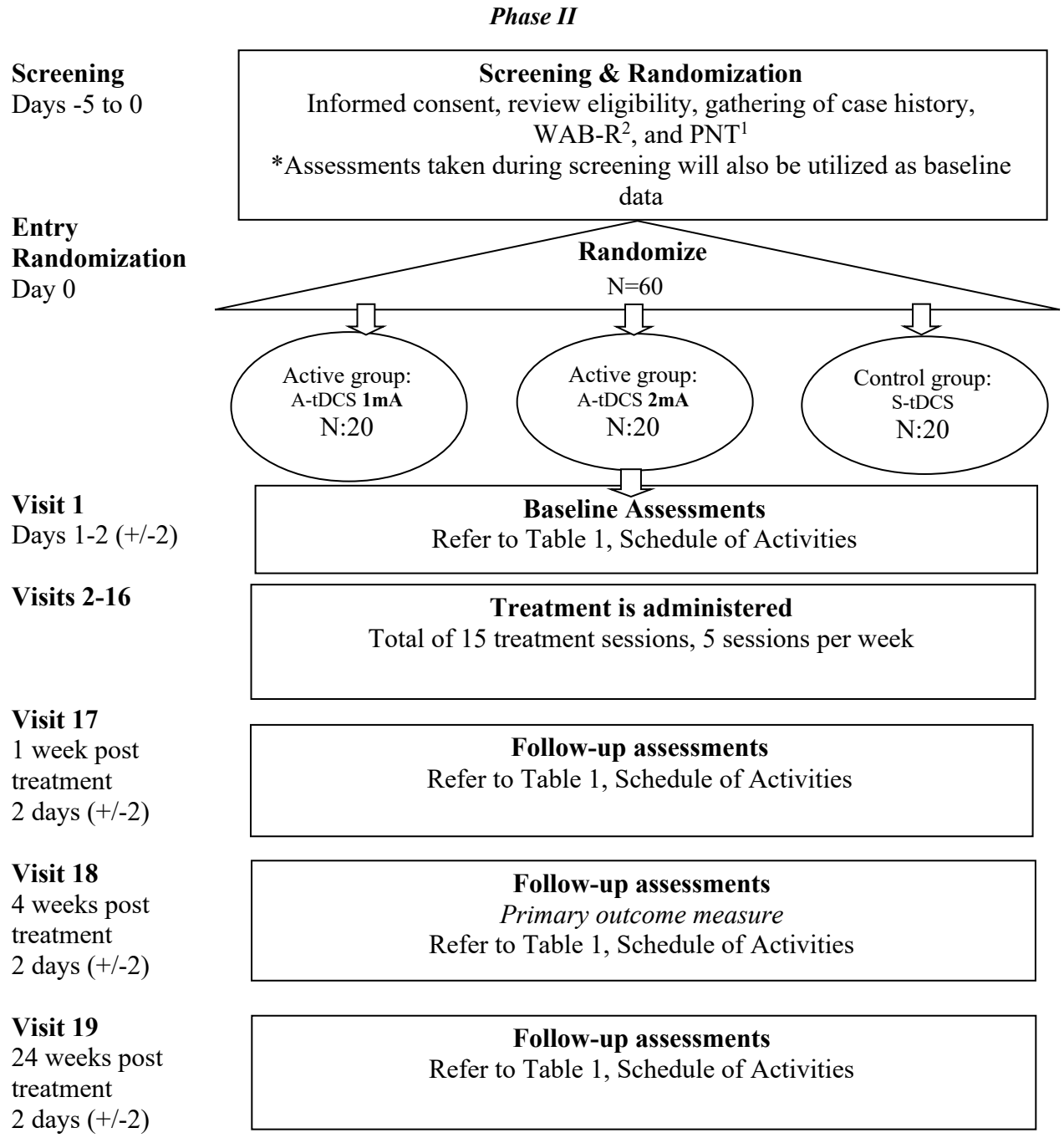
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Transcranial Direct Current Stimulation to Treat Aphasia: A Superiority Study
Study Description:	This project is a prospective randomized controlled double-blinded clinical trial to compare auditory-visual speech therapy coupled with adjuvant active anodal tDCS (A-tDCS) versus speech therapy coupled with sham tDCS (S-tDCS). We will perform an adaptive Phase II/III design, in which the first portion of the study (Phase II) will determine the optimal dose of A-tDCS (1 mA versus 2 mA) and provide a go/no-go decision for Phase III. We will use a 10-10 system to determine electrode placement, with 5 x 5 cm pads, and stimulation duration will be 20 minutes. Phase III will test the definitive superiority of adjuvant A-tDCS at the optimal dose coupled with speech therapy versus speech therapy alone (S-tDCS) to improve naming among individuals with chronic Broca's aphasia.
Objectives:	**Primary outcome measure:** The Philadelphia Naming Test (PNT)[1] will be administered once per day on two consecutive visits within each time point at baseline, 1-week post treatment, 4-weeks post treatment, and 24 weeks post treatment. The change in the number of correctly named items between the average of the two pre-treatment PNT assessments and the average of the two post-treatment PNT sessions at 4 weeks will be calculated. **Secondary outcome measures:** A) Global Aphasia severity as measured by the Western Aphasia Battery-Revised (WAB-R)[2] Aphasia Quotient (AQ); B) Functional communication as measured by the Communication Activities of Daily Living-Third Edition (CADL-3)[3] and the Communication Effectiveness Index (CETI)[4]; C) Quality of life as measured by the Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39)[5]; and D) Communication confidence as measured by the Communication Confidence Rating Scale for Aphasia (CCRSA)[6].

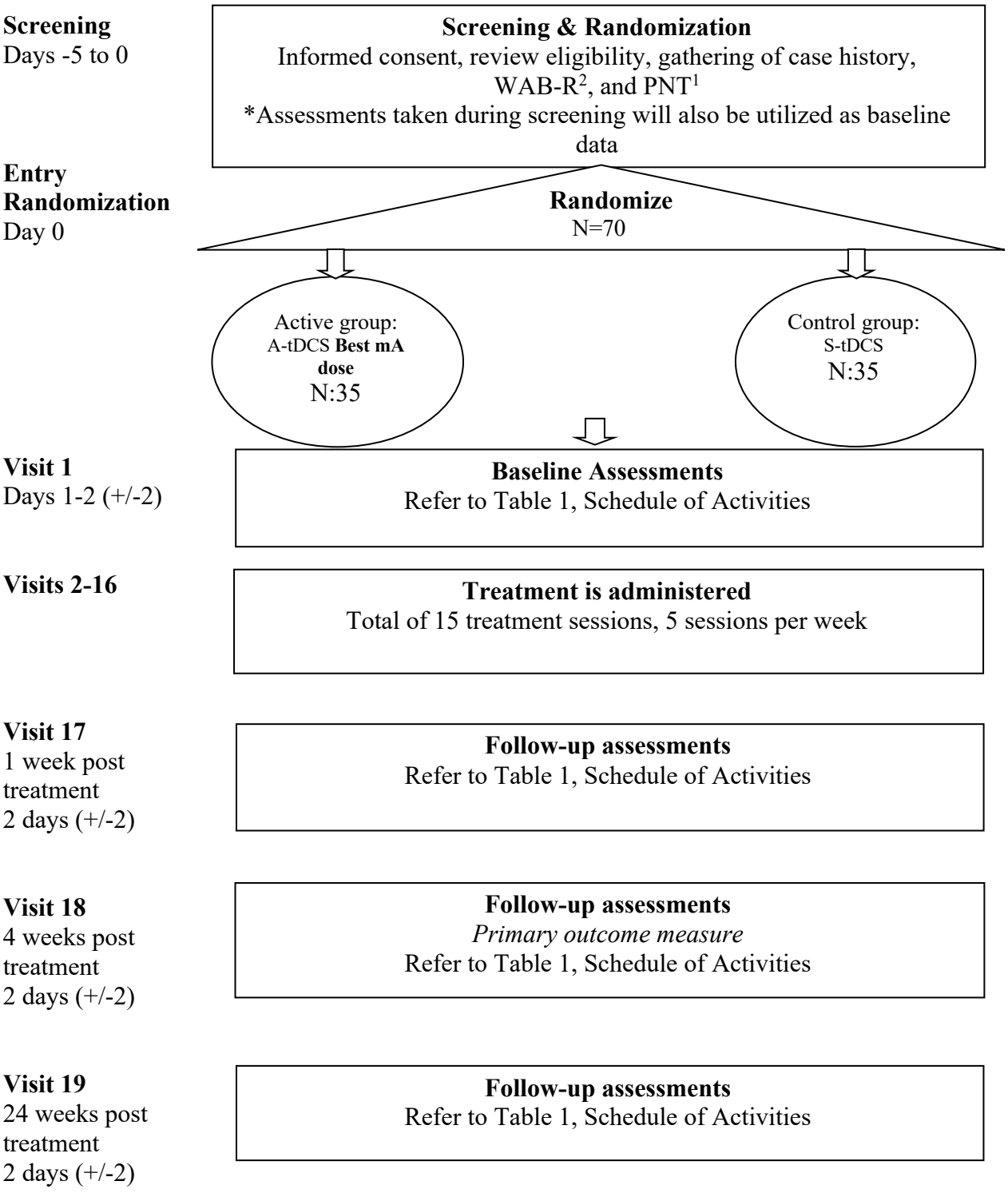
	Narrative samples will be obtained for exploratory linguistic analyses related to discourse and syntax. The change in the number of correctly named items between the average of the two pre-treatment PNT assessments and the average of the two post-treatment PNT sessions at 1 and 24 weeks will be calculated. Safety, defined as the proportion of new AEs, will be compared between groups.
Endpoints:	**Primary Endpoint**: Proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT of 9 points or more. The PNT assessment will be administered on two consecutive visits within each time point at baseline, 1-week post treatment, 4-weeks (primary endpoint) post treatment, and 24-weeks post treatment. An average number of pictures named across two administrations is calculated for each time point. **Secondary Endpoints**: For secondary measures – WAB-R AQ (aphasia severity), CADL-3 and CETI (functional communication), SAQOL-39 (quality of life), and CCRSA (communication confidence) – the endpoint will be the change in scores from baseline to 4 weeks post treatment. For secondary measure, safety, the proportion of new AEs will be compared between groups.
Study Population:	130 individuals with chronic (>6 months) post-stroke Broca's aphasia due to left hemisphere stroke between 25 and 80 years of age. 60 individuals will be enrolled in Phase II. If the study progresses to Phase III, 70 more participants will be enrolled.
Phase:	II/III
Description of Sites/Facilities Enrolling Participants:	There are 3 participating sites: Medical University of South Carolina (MUSC), University of South Carolina (USC), and University of Utah (UofU). Participants will be recruited from surrounding communities and neurology clinics located in South Carolina, Utah, or surrounding states, or affiliated with University of South Carolina (USC), the Medical University of South Carolina (MUSC), and the University of Utah.
Description of Study Intervention:	Each participant will receive a total of 15 treatment sessions, 5 sessions per week, at one hour per session; with tDCS administered for 20 minutes of each session. Each participant will receive an auditory-visual lexical therapy at each session, along with either A-tDCS or S-tDCS.
Planned Interim Analysis:	Enrollment will halt once 60 participants have been enrolled and completed the 4-week post treatment visit. An interim analysis will be performed to decide whether to proceed from Phase II to Phase III and, if Phase III is conducted, to decide on the best dose for tDCS. The study team and NIDCD may re-estimate the sample size based on the interim analysis and proceed as appropriate for Phase III.
Study Duration:	60 months
Participant Duration:	28 weeks

1.2 STUDY DESIGN



*Interim analysis will be completed following visit 18 (4-weeks post treatment/primary outcome timepoint) for 60 participants.

Phase III


Screening
Days -5 to 0
Screening & Randomization
Informed consent, review eligibility, gathering of case history, WAB-R[2], and PNT[1]
*Assessments taken during screening will also be utilized as baseline data
Entry Randomization
Day 0
Randomize
N=70
Active group:
A-tDCS Best mA dose
N:35
Control group:
S-tDCS
N:35
Visit 1
Days 1-2 (+/-2)
Baseline Assessments
Refer to Table 1, Schedule of Activities
Visits 2-16
Treatment is administered
Total of 15 treatment sessions, 5 sessions per week
Visit 17
1 week post treatment
2 days (+/-2)
Follow-up assessments
Refer to Table 1, Schedule of Activities
Visit 18
4 weeks post treatment
2 days (+/-2)
Follow-up assessments
Primary outcome measure
Refer to Table 1, Schedule of Activities
Visit 19
24 weeks post treatment
2 days (+/-2)
Follow-up assessments
Refer to Table 1, Schedule of Activities

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Study Schedule (Phase II or Phase III)

Study Activities	Screening	Day 0	Visit 1 Baseline Days 1-2 (within 1 week of treatment onset)	Visits 2-16 Treatment For 3 weeks (+/- 2 days)	Visit 17 1 week post treatment (+/- 3 days)	Visit 18 4 weeks post treatment (+/- 1 week)	Visit 19 24 weeks post treatment (+/- 1 week)	Early Study Termination Visit***
Written informed consent	X							
Case history questionnaire*	X							
Concomitant speech therapy questionnaire	X				X	X	X	
MRI safety screening	X							
tDCS safety screening	X							
Physiological measurements				X				X
Wong-Baker FACES				X				
Symptom questionnaire			X	X	X	X	X	
Randomization		X						
Treatment delivery				X				
NIH Stroke Scale			X					
CCI[11]			X					
LOFT[12]			X					
SADQ-10[13]			X					
ASRS 3.5[8]			X					
WAIS-III[9]			X					
PPTT[10]			X					
WAB-R AQ[2]	X				X	X	X	
PNT[1]	X		X		X	X	X	X
NRS-FRS Fatigue Scale			X		X	X	X	
SAQOL-39[5]			X		X	X	X	
CADL-3[3]			X		X	X	X	
CETI[4]			X		X	X	X	
CCRSA[6, 7]			X		X	X	X	
Discourse**			X		X	X	X	
Evaluation of adverse events			X	X	X	X	X	X
Best Guess****				X				
Neuroimaging								
Structural MRI (T1, T2 and DTI)	X							
Electrode positioning			X					
Review MRI scan	X							

***Case history questionnaire:** Age at the time of the stroke, sex (Male, Female), race/ethnicity (White, Black, Hispanic, etc.), education level, good family support (Yes or No), and medical history.

****Discourse measures** will be obtained following the procedures adopted in the SpARc clinical trial (Speech entrainment for aphasia recovery, ClinicalTrials.gov Identifier: NCT04364854). The procedural items are: 1) PB&J and 2) Scrambled Eggs. The participant will be provided a picture of each and will be recorded while describing each procedure. The narrative items are: 1) Cinderella and 2) Little Red Riding Hood. The participant will be provided with a picture book without text to guide and serve as a reminder of the story. Once completed, the participant will be recorded and asked to retell the story in their own words without pictures. We will employ coding analysis through AphasiaBank: Codes for the Human Analysis of Transcripts (CHAT) and Computerized Language Analysis (CLAN) to measure various discourse lexical and syntax variables.

****Early Study Termination Visit:** If electing to discontinue the study before study completion, the participant will be asked to participate in an Early Study Termination Visit prior to discontinuing the study. This visit will be offered in a virtual format as needed. Participants who express intent to terminate the trial early will be asked to continue participation for primary outcome ascertainment and safety assessment, if applicable, only. The study team will ask the participant to complete one final PNT to minimize the impact of missing data. If a participant fully withdraws from the study, a final evaluation of adverse events will be conducted and the reason for early termination will be documented.

*****Best Guess:** At the conclusion of the final treatment session, the participant and the speech-language pathologist will provide their best guess independently as to which treatment condition the participant received (active, sham). Cues for comprehension of task may be provided if needed. Only after the participant and SLP provide their best guesses, if a care partner is available, independently, their best guess will be elicited.

Components of Study Visits:

All assessment/treatment visits will be completed face-to-face.

Assessment Administration (Screening, Baseline, 1-week post treatment, 4-weeks post treatment, 24-weeks post treatment, Early Study Termination Visit)
At screening, written informed consent will be obtained prior to the completion of screening evaluations. Participants will also complete at screening: a case history questionnaire, concomitant speech therapy questionnaire, tDCS safety screening, MRI safety screening, and structural neuroimaging. In addition, the study physician will review the MRI scan to determine eligibility. The Western Aphasia Battery-Revised (WAB-R) will be administered at screening, visit 17 (1-week post treatment), visit 18 (4-weeks post treatment), and visit 19 (24-weeks post-treatment) to assess language impairment and aphasia severity. The Philadelphia Naming Test (PNT), the primary outcome measure, will be administered daily over two consecutive visits at screening/baseline for eligibility, as well as daily over two consecutive visits within each time point at visits 17, 18, and 19. Additional measures administered at baseline, visit 17, visit 18, and visit 19 include: evaluation of adverse events, symptom questionnaire, the Stroke and Aphasia Quality of Life Scale (SAQOL-39), the NRS-FRS Fatigue Scale, Communicative Activities of Daily Living-3 (CADL-3), Communicative Effectiveness Index (CETI), Communication Confidence Rating Scale for Aphasia (CCRSA), and discourse tasks (procedural and narrative). Baseline-only assessments include the Apraxia of Speech Rating Scale 3.5 (ASRS 3.5), the Wechsler Adult Intelligence Scale-III Matrix Reasoning Subtest (WAIS-III), the NIH Stroke Scale, the Charlson Comorbidity Index (CCI), the LOFT, the SADQ-10, and the Pyramids and Palm Trees Test (PPTT). The concomitant speech therapy questionnaire will also be conducted at visits 17, 18, and 19. All standardized assessments will be administered by certified speech-language pathologists (SLPs) according to manualized procedures, and scoring will be completed by SLPs and/or central raters. Rest breaks will be provided throughout assessment sessions as needed. There will be flexibility built into all the assessment visits to allow for completion over 2 days +/-2 as needed. We will have specific checklists for each visit and the order of assessments will prioritize outcome measures, but will also be balanced by rigor to reduce mental fatigue. If the participant elects to end the study early, the study team will give them the option to complete an assessment of physiological measurements (if applicable), evaluation of adverse events, and the PNT at the Early Study Termination Visit.

Table 2. Scoring and Recording of Assessments

Assessment	Video record and score	Video record, but not scored	Scorer		No video recording (some assessments may be recorded for fidelity purposes)
			Local site SLP	Centralized (USC)	
NIH Stroke Scale			X		X
CCI			X		X
LOFT			X		X
SADQ-10			X		X
NRS-FRS Fatigue Scale			X		X
WAB-R AQ Screening	X		X	X	
WAB-R AQ Visit 17, 18, 19		X		X	
ASRS 3.5	X		X		
PNT Screening	X		Scored for eligibility only	X	
PNT Baseline		X		X	
PNT Visit 17, 18, 19		X		X	
SAQOL-39			X		X
CADL-3	X		X		
CETI			X		X
WAIS-III			X		X
PPTT			X		X
CCRSA			X		X
Discourse		X		X	

Treatment Administration

Blinding and Code Assignment

An independent statistician will manage participant group assignment using a coded device system provided by Soterix Medical. Each tDCS device provided by Soterix Medical will come with codes pre-programmed on the device, and only the unblinded member will know the value of the codes. Each participant will be assigned a unique subject code corresponding to either active or sham stimulation (e.g., Subject A – Site 1 – Code 123456). This code will remain constant across all treatment sessions for that participant. Only the statistician (USC) will have access to the code assignments to maintain double-blind conditions. Investigators, site staff, and participants will remain blinded to stimulation condition throughout the study.

Electrode Positioning (Baseline/Visit 1)

Electrode placement will be individualized based on each participant's structural MRI data. The following procedures will be followed:

1. Use the standardized 10-10 EEG electrode placement system to label scalp sites and locate standard cranial landmarks (nasion, inion, preauricular points).
2. Based on calculations, locate PI provided stimulation site on scalp.
3. Once electrode placement calculations are complete, record electrode positions for use during treatment sessions.

Guidance for physiological measurements, interpretation, and response during Visits 2-16

Blood pressure, heart rate, pulse ox, and temperature will be measured immediately before and after each tDCS session (visits 2-16). Speech-language pathologists, trained by the study physician, will conduct the physical exam. Any concerning symptoms or abnormal vital signs will trigger termination of the session and prompt evaluation by the study SLP, with escalation to emergency services if necessary. The study physician remains available for consultation. Standardized procedures for repeat measurements, symptom assessment, and adverse event documentation are in place, and all staff are trained to recognize and respond to safety concerns. Although conventional tDCS protocols (≤2 mA, ≤20 minutes) have not been associated with clinically significant cardiovascular changes, pre-session measurements ensure that participants begin stimulation from a safe physiologic baseline (e.g., screening for markedly elevated blood pressure or abnormal heart rate). Post-session measurements allow detection of unexpected changes that could indicate an adverse response to stimulation. These procedures provide additional participant protection, align with best-practice safety monitoring in noninvasive brain stimulation research, and demonstrate compliance with ethical and regulatory expectations for systematic safety documentation.

Standard Procedures for Physiological/Adverse Event Screening and Monitoring

1. **Pre-session Screening**
    a. Initial blood pressure, heart rate, pulse ox, and temperature will be recorded prior to stimulation.
    b. If one of these measures are in the abnormal cut off ranges, namely:
        i. Blood pressure is **< 90/45 mmHg** or **>180/120 mmHg**
        ii. Resting heart rate **< 40 bpm** or **>120 bpm**
        iii. Pulse oximetry **< 85%**
        iv. Temperature **> 100 degrees Fahrenheit**

        a repeat measure will be taken after 5 minutes of rest.
    c. If abnormal values persist, the session will not proceed, and the study physician or licensed medical provider will be notified.
2. **Symptom Assessment**
    a. Irrespective of the physiologic measure described above, symptoms will also be checked prior to treatment.

    b. Participants will be asked about symptoms such as dizziness, headache, chest pain, palpitations, shortness of breath, nausea, fatigue, visual symptoms, altered mental status, or itching/burning at electrode site.
        i. Pain will be assessed through the Wong-Baker FACES Pain Rating Scale.
    c. The scalp location of electrode placement will be visually inspected before and after each session.
    d. Vital sign abnormalities will be interpreted in the context of the participant's medical history (e.g., chronic hypertension, baseline bradycardia) and current symptoms to determine clinical significance.
3. **Post-session Evaluation**
    a. Immediately following stimulation, blood pressure, heart rate, pulse ox, and temperature will be rechecked.
    b. If values are elevated or decreased compared to baseline, participants will rest for 4–5 minutes and a second measurement will be obtained.
    c. Abnormalities will be evaluated in the context of history and post-session symptom assessment.
4. **Criteria for Possible Adverse Events** – If any of these changes were to occur from before to after treatment
    a. Any new arrhythmia, syncope, chest pain, or concerning cardiopulmonary symptom.
    b. Blood pressure increase of **≥40 mmHg systolic** or **≥30 mmHg diastolic** from baseline that persists after repeat measurement.
    c. Heart rate **<50 bpm with symptoms** (e.g., dizziness, presyncope) or **<40 bpm regardless of symptoms**.
    d. Heart rate increase or decrease of **≥40 bpm from baseline** persisting for >2–3 minutes, monitored intermittently.
    e. Pulse oximetry **< 85%.**
    f. Temperature **> 100 degrees Fahrenheit.**
5. **Clinical Oversight and Care**
    a. If concerning values or symptoms persist, the session will be terminated.
    b. Study SLP will evaluate abnormal values/symptoms. The study physician remains available for consultation.
    c. If urgent care is warranted, emergency medical services will be activated. Otherwise, participants will be advised to follow up with their primary care provider, and, with participant permission, the provider may be notified directly.
6. **Staff Training and Escalation**
    a. All study staff will be trained to recognize problematic values and associated symptoms.
    b. Staff will follow standardized procedures for repeat measurements (as described in steps 1, 2, and 3 above), symptom evaluation, and escalation to the study physician.
7. **Documentation and Reporting**
    a. All vital signs, contextual factors (history, baseline status, and symptoms), and actions taken will be documented in the study record.
    b. Any adverse events will be documented accordingly and reported to the IRB and Data Safety Monitoring entity in compliance with study protocol.

Treatment Delivery Procedures (Visits 2–16)

Each treatment session will follow the steps below:

1. Participants will be asked about any new symptoms or changes to health since the last visit.
2. Measure and record the participant's **blood pressure, heart rate, pulse ox, temperature, and Wong-Baker FACES pain rating**. Conduct skin assessment.
3. Check tDCS device battery.
4. **Saturate sponge** by using syringe with 7.2mL (3.6mL per side) of 0.9% saline solution.

5. Repeat step 4 for second sponge.
6. Attach red/black connecting cables to carbon rubber electrodes.
7. Insert carbon rubber electrode with the flat part towards flat side of buttons on sponge.
8. Locate anode electrode position based on **electrode positioning measurements** during Visit 1.
9. Place the **anode** electrode on the left scalp over the targeted cortical region/stimulation site, and the **cathode** electrode on the scalp of the contralateral frontal region above the right eyebrow.
10. Adhere to participant's head with elastic fastener set.
11. Aim for **optimal** contact with skin.
12. During **First Treatment Visit**, take a photo of the anode electrode/sponge positioned on participant's scalp, avoiding participant's face. Upload to Dropbox.
13. Ready to setup **computerized lexical semantic therapy task**.
    - Open the therapy software on the laptop and enter the STARS participant ID.
    - Place the laptop in front of the participant.
    - Adjust volume as needed.
14. Instruct the participant how to complete the **computerized lexical semantic therapy task**, which is synchronized with stimulation:
    - Participants will view a picture followed by a video of a speaker's mouth saying a noun.
    - They will press the green button for a match and red for a mismatch.
    - Immediate visual feedback (smiley/frowny face) will be provided.
    - The program automatically records responses and displays accuracy at end of session.
15. **To begin tDCS, turn the device on by pressing power button**.
16. THEN, plug in connecting cables to appropriate color coordinating port on device.
17. Enter 5-digit code into keypad on tDCS device and press start to begin 20 minutes stimulation. Participant will be monitored during the entirety of stimulation by trained study personnel.
18. The tDCS stimulation and computerized lexical semantic therapy task will be started simultaneously.
19. **Once the tDCS is completed, unplug connecting cables.**
20. Turn off machine & take batteries out.
21. Computerized lexical semantic therapy task continues to run for a full 45 minutes.
22. After the session, again measure **blood pressure, heart rate, pulse ox, temperature, and Wong-Baker FACES pain rating**. Conduct skin assessment.
23. Complete Symptom Questionnaire.
24. **Document any adverse events** reported during or since the last visit.

Optional Home-Based Study Activities
To support participant retention and operational flexibility, study activities may be conducted in the participant's home when appropriate and feasible.

All home-based study activities will be performed by appropriately trained and qualified study personnel in accordance with the protocol, applicable standard operating procedures, Good Clinical Practice, and relevant privacy and safety requirements. Any data collected during home-based activities will be documented, handled, transported, and stored in accordance with protocol requirements and applicable regulations. Participation in home-based activities will be optional.

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic aphasia is a language processing impairment that persists for more than 6 months after a stroke, affecting 2 million people in the United States [14, 15]. Chronic aphasia is strongly associated with

depression, low quality of life, and social isolation[16, 17, 18]. Speech therapy can lead to language improvements in chronic aphasia, but its results are often limited and unsatisfactory[19-23].

Given that 1) individuals with post-stroke chronic aphasia have the potential to improve, and 2) speech therapy alone has limited efficacy[19-23], there is a strong need for adjuvant approaches to improve outcomes. Brain stimulation with transcranial direct current stimulation (tDCS) has emerged as a promising, non-invasive, and accessible approach. Several pilot studies have demonstrated that adjuvant tDCS, when coupled with speech therapy, may enhance therapeutic effects[24-28]. However, the existing tDCS literature in aphasia consists primarily of non-controlled studies with small sample sizes and limited clinical power[29]. Unfortunately, these studies do not yet provide sufficient or definitive evidence of tDCS effectiveness to justify its translation into clinical use[30]. This knowledge gap represents a significant barrier to seizing a rare opportunity to introduce a potentially impactful therapy for individuals with aphasia. Thus, there is an urgent need for a definitive clinical trial to prove or disprove the efficacy of adjuvant tDCS for chronic aphasia.

2.2 BACKGROUND

Our team completed the necessary steps to guide and support a definitive trial, including conducting a Phase II tDCS futility trial in which we: 1) confirmed that a definitive tDCS trial is not futile, 2) validated the tDCS approach, and 3) identified Broca's aphasia as the optimal responder group[24]. We now propose a final prospective randomized, controlled, double-blinded, adaptive Phase II/III clinical trial to confirm the optimal tDCS dose and demonstrate its superiority.

The outcome measure will focus on improvement in naming ability as measured by the Philadelphia Naming Test (PNT)[1]. The primary endpoint will be the proportion of "responders" where "responder" is defined as a change in average number of pictures named on the PNT of 9 points or more. The PNT assessment will be administered on two consecutive visits for each time point at baseline, 1-week post treatment, 4-weeks post treatment (primary endpoint), and 24-weeks post treatment. An average number of pictures named across two administrations is calculated for each time point.

In addition, we will test aphasia severity, functional communication, communicative effectiveness, quality of life, and narrative samples for exploratory linguistic analyses to explore improvement from baseline to 4 weeks post-treatment in other aspects of language.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks and Discomforts. For this research project, there are four areas of interest regarding the protection of human subjects: 1) potential adverse effects associated with tDCS administration; 2) potential adverse effects associated with MRI scanning; 3) potential adverse effects associated with behavioral testing and treatment; and 4) maintenance of participant confidentiality. Each of these items is addressed below:

1. **tDCS administration**. The tDCS used in this trial is investigational and the Investigational Brochure is attached to this document below. The device was determined by the USC IRB to be non-significant risk. tDCS is a non-invasive approach to stimulate the cortex and modulate cortical activity through a continuous weak polarizing electrical current. In this current study, we will use the Soterix Transcranial Electrical Stimulation for Clinical Trials device (Soterix Medical Inc., New York), which is an integrated tDCS hardware platform device commonly used in tDCS clinical trials across multiple specialties and conditions[32-36]. This project will utilize 1 mA or 2 mA of active tDCS (A-tDCS) stimulation (depending on the study arm) induced between two 5 x 5 cm saline-soaked sponges, where one sponge (anode) is

placed on the left scalp over the targeted cortical region, and the other (cathode) is placed on the scalp of the contralateral frontal region above the right eyebrow. A-tDCS stimulation will start at the same time as the computerized lexical semantic therapy task begins and last for 20 minutes during the treatment sessions for the experimental group. To date, no serious adverse effects of tDCS have been reported in the literature when safety guidelines are followed[39, 40]. In a meta-analysis[40], the following effects were reported during 567 tDCS administrations in 102 participants over two years: 1) 70% noticed a mild tingling under the electrodes; 2) 35% felt fatigue following treatment; and 3) 30% felt itching under the electrodes. The tingling and itching sensations were almost always reported as being transient. Additionally, headache (11%), nausea (3%), and insomnia (1%) were reported. Note that this review did not distinguish between 1 mA and 2 mA stimulation or between 20 min and 30 min of stimulation, the two most common current and time dosages used in human research, respectively. The current project will only administer 1 mA or 2 mA for 20 minutes per treatment session. It is important to note that tDCS does not cause significant heating effects under the electrodes, alter the blood-brain barrier, or induce edema[41]. Testing of cognitive and motor abilities following stimulation has not resulted in any significant deficits. In stroke patients, tDCS has been associated with improvements in motor performance[44, 45] and naming abilities[27]. Among more than 80 participants enrolled in our previous studies,[24, 37, 38] no negative effects associated with tDCS administration beyond mild tingling at the beginning of the treatment session were reported. The clinician who is in charge of setting up and monitoring the treatment session will enter ratings from the Wong-Baker FACES[43] scale to the online interface maintained by the Data Core. In our previous futility clinical trial, no serious adverse events were associated with A-tDCS. Using the same time and current stimulation parameters (20 min and 1 mA), participants were assessed at the end of each treatment session for adverse events, vital signs, and discomfort ratings using the Wong-Baker FACES Pain Rating Scale[43]. There were no statistically significant differences in adverse events between participants receiving active vs. sham stimulation (A-tDCS vs. sham-tDCS)[24]. All participants enrolled in this project will be evaluated at the end of each week of treatment by a certified speech-language pathologist (SLP) with expertise in aphasia and stroke. Before the study initiation, the SLPs will be trained by Dr. Bonilha in the administration of the NIH stroke scale, and how to identify new neurological signs and symptoms.

2. **MRI scanning.** We have conducted extensive research using MRI in stroke. Overall, the number of stroke patients who have received MRI in our studies exceeds 250. Among participants with chronic stroke who have participated in our research, we have occasionally had to exclude participants because of factors contraindicated to MRI. Interestingly, we have observed that some participants who have experienced negative reactions to clinical MRI sessions did not have problems with research MRI since the environment is somewhat different. We find that most participants who have reported negative reaction to past MRI experiences do not have problems with our MRI setup. The MRI scanners used for this research are 3T short-bore magnets with a wider bore than most older generation scanners. This allows the participant rather easily to see through either end of the scanner bore without shifting head position. For the tDCS electrode placement, each participant will undergo one pre-treatment MRI session. We will perform thorough screening to check for factors contraindicated to MRI scanning (e.g., metal implants, pregnancy, pacemaker, severe claustrophobia). We will follow the same protocol that we have used with past participants. First, each person fills out a questionnaire in collaboration with a clinician and, when needed, a legally authorized representative (LAR). Then, we give each participant ample time to become familiar with the scanner (we show them the stimulus presentation hardware, the computer console, and the headphone/microphone used to record speech) before the actual scanning session starts. We find that taking this extra time to familiarize participants and, when appropriate, family members with the MRI setup usually helps participants feel comfortable with the MRI session. For participants who may not be able to perform a new research scan secondary to *claustrophobia, practical limitations related to scanning availability,* or *incompatibility with scanning (e.g., metal implants),* we will allow for the use of any past clinical MRI scan, as long as there has been no other clinical episode since. We will require the ability to see the actual image from the scan, along with the report, in order to use a previous scan.

3. **Participant testing/behavioral treatment.** In our experience, some participants can have a negative reaction to language and cognitive testing. For example, this can occur when participants realize that their performance on a given test is far worse than they would have expected. We always make sure that ample time is allotted for testing and that participants are allowed breaks as needed. So far, we have never had a participant discontinue study participation because of an adverse reaction to study testing. Almost without exception, participants who participate in our treatment studies wish to continue study participation even when the treatment period has expired, as it allows them access to aphasia treatment. Concerning the behavioral treatment, the only adverse reaction that we occasionally see in our treatment studies is fatigue. This is something about which we warn participants ahead of time, and we have not experienced fatigue being a reason for A-tDCS treatment discontinuation.

4. **Participant confidentiality**. All study personnel will be obligated to ensure that the confidentiality of personal and medical identifiers is always maintained. The sites will follow privacy obligations under the Health Insurance Portability and Accountability Act (HIPAA). Because the Data Core uses a web-based system, source documents will remain at each site. The study database and any study documents submitted to the Data Core will only identify study subjects by unique study identification codes. All data will be stored in a manner that is HIPAA compliant, without the ability to track the information back to a specific subject except through a password-protected system. Subject information will be stored by a unique identification code.

2.3.2 KNOWN POTENTIAL BENEFITS

All participants enrolled in this research will receive behavioral aphasia treatment that can improve naming ability[24]. Few patients with chronic aphasia receive speech therapy. Furthermore, many study participants (the active arms) will receive A-tDCS, which may further enhance the behavioral effect of aphasia treatment.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

See Soterix Transcranial Direct Current Stimulator Clinical Trials operator's manual for additional information about the Soterix tDCS device.

The risks associated with study participation are low and manageable, particularly when compared with the potential benefits of improved aphasia treatment. The most relevant risks are those associated with tDCS administration, MRI scanning, behavioral testing, and data confidentiality. These risks have been carefully addressed in the study design.

tDCS risks are minimal and limited to transient skin sensations such as tingling or itching. These effects are well-documented, mild, and have been experienced without consequence in our prior studies using the same or similar devices and stimulation protocols. No serious adverse events have been reported across hundreds of sessions. Use of the Soterix device provides additional safety through real-time impedance monitoring and operator alerts via SMARTscan technology. Safety is further enhanced by consistent adherence to standard stimulation parameters (1–2 mA, 20 min), which have been used extensively in stroke and aphasia research without complication.

MRI scanning will be limited to a single pre-treatment session per participant and will follow established screening procedures to exclude individuals with contraindications (e.g., pacemakers, metal implants, or claustrophobia).

Behavioral testing may cause frustration or emotional discomfort due to the nature of cognitive and language assessments, but participants are offered breaks, reassurance, and supportive interactions throughout the process. Fatigue, while occasionally reported, has never led to treatment discontinuation in our previous studies.

The study employs stringent measures to protect participant confidentiality, including web-based data entry platforms managed by the Data Core, secure storage of all data, and the use of unique identifiers in place of personal information.

The necessity of exposing participants to these minimal risks is justified by the potential benefits. tDCS represents a promising adjuvant therapy for improving language recovery in individuals with chronic aphasia, which is an area where current standard treatments show limited efficacy. Given that participants in the chronic stage of aphasia retain capacity for neuroplastic recovery, yet often lack access to effective treatment options, this trial has the potential to directly impact future clinical practices. Moreover, the trial builds on rigorous pilot work and a completed Phase II futility study that confirmed feasibility and safety of this approach.

In summary, the risk-to-benefit ratio is favorable. Risks are low, well-characterized, and minimized through careful design and monitoring. The potential benefit of improved therapeutic outcomes for individuals with chronic aphasia justifies the inclusion of these minimal risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Phase II Primary		
To select the dose of tDCS for phase III of the study that has the highest effect size on improvement in **naming** at 4-weeks post treatment.	Proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT assessment of 9 points or more from baseline to 4-week post treatment time point. The PNT will be administered on two consecutive visits at baseline and at 4-weeks post treatment and scores at each time point are averaged.	Anomia is a core deficit in Broca's aphasia[46, 47] and is strongly linked to lower quality of life and functional communication[48, 49].
Phase III Primary		
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **naming** at 4-weeks post treatment.	Proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT assessment of 9 points or more from baseline to 4-week post treatment time point. The PNT will be administered on two consecutive visits at baseline and at 4-weeks post treatment and scores at each time point are averaged.	Anomia is a core deficit in Broca's aphasia [46, 47] and is strongly linked to lower quality of life and functional communication [48, 49].

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
Secondary		
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **naming** at 1-week post treatment.	Proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT assessment of 9 points or more from baseline to 1-week post treatment time point. The PNT will be administered on two consecutive visits at baseline and at 1-week post treatment and scores at each time point are averaged.	Anomia is a core deficit in Broca's aphasia [46, 47] and is strongly linked to lower quality of life and functional communication [48, 49].
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **naming** at 24-weeks post treatment.	Proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT assessment of 9 points or more from baseline to 24-week post treatment time point. The PNT will be administered on two consecutive visits at baseline and at 24-weeks post treatment and scores at each time point are averaged.	Anomia is a core deficit in Broca's aphasia [46, 47] and is strongly linked to lower quality of life and functional communication [48, 49].
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in reducing **Aphasia severity** as measured by the WAB-R AQ score.	Change in WAB-R AQ score from baseline to 4-week post treatment time point.	To assess overall improvement in receptive and expressive language skills that are often impacted in people with Broca's aphasia.
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **functional communication.**	Change in scores on CADL-3 and CETI from baseline to 4-week post treatment time point.	To assess if gains from treatment are related to gains in functional communication abilities (e.g., increased participation in conversations related to daily living).
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **quality of life** as measured by the SAQOL-39.	Change in SAQOL-39 score from baseline to 4-week post treatment time point.	To assess if gains from treatment are related to improvements in quality of life.

OBJECTIVES	*ENDPOINTS*	*JUSTIFICATION FOR ENDPOINTS*
To demonstrate superiority of active tDCS with speech therapy compared to sham tDCS with speech therapy in improving **communication confidence**.	Change in CCRSA score from baseline to 4-week post treatment time point.	To assess if gains from treatment are related to increased confidence communicating.
To demonstrate **safety** differences between groups.	Proportion of new adverse events.	To assess the safety of tDCS in a clinical setting.
Exploratory		
Improvement in discourse tasks with active tDCS with speech therapy compared to sham tDCS with speech therapy.	We will have the opportunity to explore other discourse lexical and syntax variables, such as change in words per minute (WPM) and verbs per minute (VPM).	To assess if gains from the treatment are related to improvements in functional language and connected level language tasks.
Sex as a biological variable.	The difference between males and females in the change in average number of pictures named on PNT assessment of 9 points or more from baseline to 1-week, 4-weeks, and 24-weeks post treatment time point.	To date, we have not observed sex related differences in aphasia therapy outcomes, but we will evaluate sex as a biological variable in this clinical trial.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, multi-site, randomized, double-blinded, placebo-controlled, adaptive Phase II/III clinical trial designed to evaluate the efficacy of adjuvant anodal transcranial direct current stimulation (A-tDCS) in combination with auditory-visual speech therapy for individuals with chronic Broca's aphasia. The study will be conducted at three sites- the University of South Carolina, the Medical University of South Carolina, and the University of Utah. The trial tests the hypothesis that speech therapy coupled with A-tDCS will lead to superior improvements in naming ability compared to speech therapy coupled with sham stimulation (S-tDCS). In Phase II, participants will be randomized 1:1:1 to receive either 1 mA A-tDCS, 2 mA A-tDCS, or S-tDCS, with the goal of determining the optimal dose of stimulation. Following an adaptive analysis and a go/no-go decision point, Phase III will proceed with a 1:1 randomization comparing the selected optimal dose of A-tDCS to S-tDCS. The study treatment duration will consist of 15 treatment sessions, 5 sessions per week over three consecutive weeks, at one hour per session. Each treatment session will include a 45-minute computerized lexical semantic therapy task, with tDCS administered during the first 20 minutes of the computerized lexical semantic therapy task. The computerized lexical semantic therapy task and tDCS stimulation will begin at the same time.

The study employs a superiority design and uses several methods to minimize bias, including double-blinding of participants and therapists, central randomization stratified by site, age, and aphasia severity (WAB-AQ), and the use of sham-tDCS as a placebo control. Sham stimulation has been shown in our prior work to maintain blinding integrity. Group allocation will remain concealed from study personnel and participants, and outcomes will be assessed by blinded raters. An interim analysis is planned at the end of Phase II to determine the optimal A-tDCS dose and decide whether to proceed to Phase III (see Section 9.4.6, Planned Interim Analysis). Stratification will be based on enrollment site, age, and baseline aphasia severity (see Section 9.4.7, Sub-Group Analyses).

The intervention in this trial is anodal tDCS delivered at either 1 mA or 2 mA (Phase II) and at the optimal dose selected for Phase III. Stimulation targets the residual posterior left temporal lobe, guided by individual MRI and EEG 10–10 positioning. The control condition, S-tDCS, provides no cortical stimulation but simulates physical sensations to preserve blinding.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Participants in the control group will receive sham transcranial direct current stimulation (S-tDCS), which includes a brief period of stimulation at the start of each session to maintain blinding. Both the sham and active stimulation groups will complete 15 sessions of auditory-visual speech therapy. In a previous futility study[24, 42], 24% of participants in the S-tDCS group and 53% in the A-tDCS group showed improvement, corresponding to 3.60 times greater odds of a good outcome with A-tDCS compared to S-tDCS. The current study was designed to define the optimal dose of A-tDCS when paired with speech therapy, with the goal of advancing to a fully powered superiority trial to evaluate treatment efficacy.

4.3 JUSTIFICATION FOR DOSE

The route of administration for this trial is transcranial direct current stimulation (tDCS), delivered via saline-soaked sponge electrodes placed on the scalp to target cortical language areas, specifically the residual posterior left temporal lobe, guided by individual MRI and EEG 10–10 positioning. The planned dosing regimen consists of daily 20-minute sessions of active or sham tDCS paired with auditory-visual speech therapy over three consecutive weeks (15 sessions total).

The Phase II portion of this trial includes a dose-confirmation stage to determine the optimal stimulation intensity. Participants will be randomized in a 1:1:1 ratio to receive either 1 mA A-tDCS, 2 mA A-tDCS, or sham tDCS (S-tDCS), each paired with standardized speech therapy optimized for Broca's aphasia. The rationale for this dosing range is informed by both prior studies and recent literature. Our earlier Phase II futility trial used 1 mA A-tDCS and demonstrated feasibility and safety. However, emerging evidence from recent tDCS studies in stroke recovery, including those cited in the 2019 and 2020 Cochrane reviews[29, 44], suggests that 2 mA stimulation may offer additional benefits, particularly for motor and language recovery. Of 21 studies in the 2019 Cochrane review on aphasia, 8 used 2 mA stimulation, and 32 of 68 studies in the 2020 review on general stroke recovery also employed 2 mA.

Higher intensities of tDCS (>2 mA) are not advisable due to increased risk of scalp discomfort (itching, burning) that can compromise participant blinding and reduce tolerability. Thus, 2 mA represents the upper limit of tolerable and effective dosing supported by the existing literature. The use of both 1 mA and 2 mA in this trial will allow for a direct head-to-head comparison to identify the optimal therapeutic dose while minimizing risk to participants.

This adaptive design provides scientific and ethical advantages by enabling early termination if a low effect size is observed in Phase II and allowing the study to proceed into Phase III using the most promising dose. This dose-optimization component is a key innovation of the current trial and will provide critical data to guide future therapeutic use of tDCS in post-stroke aphasia.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all visits of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SOA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SOA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants in this study will have chronic stroke-induced aphasia. Diagnostic evaluations will be conducted during the participants' initial visit to confirm aphasia diagnosis. Participants currently receiving speech and language therapy will be required to temporarily discontinue involvement until study completion. A study team member will collect data from participants about participation in speech therapy during screening and all follow up visit time points.

Participants must satisfy the following inclusion criteria to be considered eligible for entry into this study:

1. Be willing and able to give informed consent.
2. Be willing and able to comply with study requirements.
3. Be between 25 and 80 years of age.
4. Have used English as the primary language for > 15 years.
5. Have the diagnosis of aphasia due to a left hemisphere stroke, confirmed by study physician based on past clinical MRI scan or research scan.
6. Be greater than 6 months post-stroke.
7. Have Broca's aphasia diagnosed by the WAB-R (fluency score ≤ 5, auditory verbal comprehension score 4-10, repetition score 0-7.9, naming and word finding score < 9).
8. Correctly name 140 or fewer items on the PNT.

5.2 EXCLUSION CRITERIA

Participants with any of the following characteristics will not be eligible for entry into this study:

1. History of brain surgery except for during the treatment of the acute stroke.
2. Seizures during the previous 12-months.
3. Compromised skin at or near electrode sites (e.g., rash, eczema, wounds, infection).
4. Correctly name more than 140 out of 175 items during the pre-treatment picture naming test (Philadelphia Naming Test).
5. Western Aphasia Battery–Revised Aphasia Quotient (WAB-R AQ) score of 25 or below*.
6. Participants with open skull defects (e.g., greater than 1 cm) in the area underneath the anode electrode positioning (due to the possibility of direct cortical overstimulation)** or participants with metal implants or electrical stimulators (due to the possibility of heating)***.
7. Participants with continuous oxygen therapy which cannot be discontinued for more than 1 hour.

8. Any condition or situation that the PI determines would significantly interfere with the participant's ability to complete the study.

*Participants with very severe aphasia will be excluded. This decision is based on the clinical understanding that individuals with extremely severe language deficits are less likely to benefit from tDCS. By excluding these cases, we will not shrink the total pool of participants with Broca's aphasia, which are usually not this severe, but rather create a more homogeneous study population where the treatment effect can be measured more reliably. This approach not only ensures that our results are interpreted better but also increases the likelihood that any observed improvement is clinically meaningful.

**Of note, no serious adverse events have been reported in the limited published experience with tDCS in participants with skull defects or cranioplasty. One case report documented successful treatment without adverse effects in a participant with severe brain damage, ventriculoperitoneal shunt, and titanium mesh cranioplasty.[59] A pediatric stroke study including one participant with prior craniectomy reported no major adverse events and good tolerability.[60] The broader tDCS safety literature (>33,200 sessions using conventional protocols ≤40 minutes, ≤4 mA, ≤7.2 Coulombs) has not produced serious adverse effects or irreversible injury, though this dataset includes minimal representation of participants with skull defects.[61] Common mild adverse effects in general tDCS populations include itching (39.3% active vs 32.9% sham), tingling (22.2% vs 18.3%), and headache (14.8% vs 16.2%).[62]

*** In participants with implantable electrical devices, we will consult with the appropriate medical team to determine risk on an individual basis.[65]

Transcranial direct current stimulation (tDCS) is not contraindicated with antidepressants, including selective serotonin reuptake inhibitors (SSRIs), and has been safely combined with these medications in multiple large randomized controlled trials.[63, 64]

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle considerations are not applicable to this study.

5.4 SCREEN FAILURES

The following screening procedures will be performed:

A signed and dated informed consent form will be obtained from each participant before conducting any screening procedures. Participants will then be assigned an identification number for the purposes of initial screening. The following questionnaires and assessments will be completed in order to determine if the participant qualifies for the study:

1. Review inclusion/exclusion criteria
2. Concomitant speech therapy questionnaire
2. Case history questionnaire
3. Administer the tDCS safety screening
4. Administer the MRI safety screening
5. Administer the WAB-R AQ
6. Administer the PNT
7. Complete MRI or obtain previous clinical MRI
8. Review MRI scan to determine eligibility

Participants who do not meet the inclusion criteria will not be enrolled in the study. Data collected will be maintained as needed for reporting screen failures. All screen failures will be documented per IRB regulations.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will enroll 130 individuals with chronic Broca's aphasia (stroke onset >6 months), between the ages of 25 and 80. Participants will be recruited from surrounding communities and neurology clinics located in South Carolina, Utah, or surrounding states, or affiliated with University of South Carolina (USC), the Medical University of South Carolina (MUSC), and the University of Utah (UofU).

All three study sites have a proven track record of recruiting participants with post-stroke aphasia. Our team has conducted multiple successful aphasia studies across these sites over the past two decades, developing adaptive, site-specific recruitment practices. Historically, we have enrolled approximately one-two new participants per site per month. Approximately 40% of individuals in our prior studies with chronic aphasia present with Broca's aphasia, supporting the feasibility of reaching target enrollment.

The first year of the project will focus on infrastructure development: hiring and training study personnel, developing the web-based data management system, procuring equipment, training Speech-Language Pathologists on treatment and assessment protocols, training graduate student outcome raters, and scheduling initial assessments. Following this preparatory phase, we anticipate enrolling 1.1–1.2 participants per site per month. The final six months will focus on data analysis and dissemination of findings.

Recruitment strategies will include:

- Targeted advertisements and social media outreach;
- Community partnerships and support group engagement (USC, MUSC, and UofU);
- Distribution of aphasia-friendly flyers at hospitals and clinics;
- Collaboration with physicians and professionals at each site;
- Use of centralized databases, including a large registry of >250 individuals with chronic aphasia (C-STAR) and access to the RESTORE research registry in Charleston and Prisma Health research registry being established by Dr. Bonilha.

Inclusion and Accessibility

Many participants will experience physical or sensorimotor disabilities post stroke. Our team is trained in inclusive practices and communication strategies for working with people with aphasia and their families. To support inclusive recruitment and participation, the investigative team has:

- Partnered with local leaders, community organizations, and support groups to address participation barriers;
- Implemented targeted outreach that has increased enrollment of African American individuals and women in recent trials (e.g., SpARc);
- Accessed support from the Center for Clinical and Translational Science Recruitment & Retention Shared Core (RRSC) and its Research Participant Advocacy Program to reach elderly, minority, and low-income populations.

Study Participant Retention

We will apply proven strategies from our prior studies to maintain participant engagement, including:

1. **Communication Training:** All study personnel will receive training in aphasia-friendly communication and are screened for suitability to work with this population.

2. **Consistent Contact:** Each participant is assigned a primary contact to simplify communication and minimize confusion.
3. **Study Branding:** We utilize a consistent study identity (e.g., logo, typography) across all materials to improve message recognition and enhance participant engagement[18].
4. **Aphasia-Friendly Materials:** Participants receive a packet that includes an aphasia-friendly study explanation and a personalized calendar of sessions.
5. **Reminders:** Study staff will provide regular appointment reminders via preferred method of communication.
6. **Responsive Support:** Personnel are trained to respond promptly to participants and their families, ensuring all questions and concerns are addressed[50, 51].
7. **Respectful Environment:** Each session is conducted in a supportive, unhurried manner to respect participants' needs and maximize data quality.

Community Engagement and Monitoring
Ongoing engagement activities include:

- Monthly communication support groups (e.g., MUSC Charleston group);
- University-based outreach programs such as annual aphasia community events, Lunch Bunch program, ambassador-led initiatives, newsletters, and a virtual recovery group.

The Program Manager will closely monitor recruitment and retention metrics throughout the trial and adapt strategies as needed to meet goals.

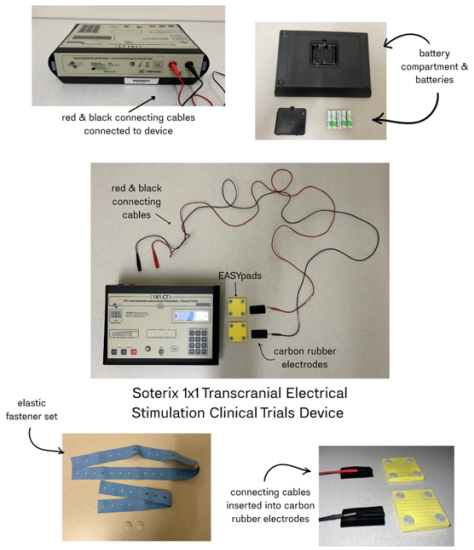
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

A trained study speech-language pathologist will administer study interventions. The study intervention will be delivered using the Soterix 1x1 Transcranial Electrical Stimulation Clinical Trials device (Soterix Medical Inc., New York), an integrated hardware and software platform widely used in tDCS clinical trials across multiple conditions. The device is investigational and is currently designed for investigative purposes until further regulatory clearance is established. Based on the published literature regarding safety, risks, and applications, and given the low dosage and voltage used in this protocol, we received IRB determination that the device qualifies as a Non-Significant Risk (NSR) device. The stimulator is a portable, battery-operated unit and supplied with EASYpads sponge electrodes (5 × 5 cm saline-soaked sponges with carbon-rubber electrodes), shielded red and black connecting cables, and elastic fastener set for electrode placement. During active stimulation (A-tDCS), current is delivered between two electrodes, with the anode positioned on the left scalp over the targeted cortical region and the cathode positioned on the scalp of the contralateral frontal region above the right eyebrow. Stimulation is initiated at the same time as the computerized lexical semantic therapy task (developed from Fridriksson's computerized anomia treatment[31, 38]) and remains active for 20 minutes of the session. Participants will receive stimulation five days per week for three consecutive weeks. Sham stimulation at 2mA (S-tDCS) will mimic the scalp sensations of active stimulation by ramping current for 30 seconds before automatic shut-off, ensuring participant blinding. The Soterix platform incorporates a double-blinded hardware–software system that allows seamless switching between A-tDCS and S-tDCS without participant or investigator intervention.

Please see below for labeled diagram of device components.



Validation and safety of this device are supported by extensive peer-reviewed literature, with adverse effects typically limited to mild, transient sensations of itching or tingling at the electrode site during the first 15–20 seconds of stimulation.

Additional information is provided in the device brochure.

The self-administered computerized lexical semantic therapy task (developed from Fridriksson's computerized anomia treatment[31, 38]) consists of a spoken word–picture matching task occurring concurrently with the application of tDCS. Prior to the initiation of treatment, the participant is provided with explicit directions regarding the task, and that is to determine if the displayed picture matched the subsequent spoken word. If the pair represent a match, the participant would press the green button, and in the case of a non-match, the participant would press the red button. The next picture would not be displayed until a response was recorded. Immediate feedback will be provided following a response in the form of a "smiley face" for correct answers and a "frowny face" for incorrect answers. Additionally, following the completion of a treatment session, a data file of the participant's responses will be automatically saved, and the accuracy score from that session will be displayed on the computer screen.

This intervention has been considered non-significant risk by full board review from the University of South Carolina IRB. The University of South Carolina IRB will serve as the parent IRB in this study, which will utilize a single IRB.

6.1.2 DOSING AND ADMINISTRATION

In Phase II, participants will be randomized 1:1:1 across the three stimulation conditions (1 mA A-tDCS vs. S-tDCS vs. 2 mA A-tDCS) with 20 participants assigned to each arm. In Phase III, participants will be randomized 1:1 to the best-performing active dose (determined from Phase II) versus S-tDCS with 35 participants assigned to each arm. In all arms, stimulation will be paired with 15 daily one-hour sessions (five days per week over three consecutive weeks). tDCS will be administered once per treatment session, for a total of 20 minutes per session, beginning at the same time as the computerized lexical semantic therapy task. Current will be delivered via saline-soaked sponge electrodes placed according to the procedures outlined in section 1.3. The therapeutic "dose" of stimulation is therefore defined by both

current intensity (1 mA or 2 mA) and cumulative exposure across 15 sessions. Sham stimulation will follow identical procedures, including ramp-up, but current will be discontinued after 30 seconds to preserve blinding.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Soterix Medical 1x1 tDCS Clinical Trials Stimulator and accessories (including EASYpads sponges, carbon-rubber electrodes, connecting cables, and headband set) will be provided directly by the manufacturer, Soterix Medical Inc., as an investigational device. Devices will be inspected prior to use, stored under appropriate conditions. EASYpads are single-use only and will be disposed of in standard waste after each session. Expired, damaged, or malfunctioning equipment will be returned to the manufacturer for servicing or disposal in accordance with manufacturer guidelines.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The study treatment is the Soterix Medical 1x1 tDCS-CT Stimulator, manufactured by Soterix Medical Inc. (New York, USA). The device is a portable, battery-operated stimulator (dimensions: 11” x 8” x 3.5”). It features labeled front- and back-panel controls, including START, ABORT, and PAUSE/RESTART functions, as well as LED displays for electrode contact quality. The system is supplied with EASYpads, carbon-rubber electrodes, output connecting cables, and elastic fasteners. Packaging is clearly labeled as “Investigational Device. Federal (or United States) law limits device to investigational use.”

6.2.3 PRODUCT STORAGE AND STABILITY

The stimulator must be stored between 50°F–110°F (10–43°C), at relative humidity between 20–90%, and atmospheric pressure 700–1060 hPa. The device must be kept dry, away from fluids, and protected from heat sources. Sponges (EASYpads) are single-use and must remain evenly moist with saline during stimulation; they are stable for one session only and must be discarded after use. Batteries should be replaced when the low-battery indicator appears. Depleted batteries must be disposed of according to local regulations.

6.2.4 PREPARATION

Study staff will prepare the device before each session. This includes inserting fresh batteries as needed, connecting color-coded electrode cables, and inspecting electrodes and sponges. EASYpads sponges are soaked with saline before electrode insertion and application to the scalp. Electrodes are secured using Soterix headband set, ensuring smooth contact without direct skin exposure to the rubber insets. The SET-UP CONTACT QUALITY feature assists in confirming electrode-skin impedance prior to stimulation. Once contact quality is verified and the subject code is entered, stimulation is initiated with the START button.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized using a secure, centralized system developed and managed by the Data Core Unit within the Division of Epidemiology and Biostatistics at the University of South Carolina

(USC), which will serve as the Statistics and Data Core Center for the trial. In Phase II, participants will be randomized in a 1:1:1 ratio to one of three arms: anodal tDCS at 1 mA (A-tDCS 1 mA), sham stimulation (S-tDCS), or anodal tDCS at 2 mA (A-tDCS 2 mA). In Phase III, participants will be randomized in a 1:1 ratio to either the optimal dose of A-tDCS (determined from Phase II) or S-tDCS. Randomization will be stratified by enrollment site, age, and aphasia severity as measured by the Western Aphasia Battery–Aphasia Quotient (WAB-AQ). Adaptive randomization will be used to maintain covariate balance across groups (see Section 9, Statistical Considerations).

Randomization will be implemented via a web-based electronic data capture system. Study personnel (e.g., the research speech-language pathologist) will input baseline and eligibility data into the Data Core's online platform prior to enrollment. If eligibility is confirmed, the system will generate a unique participant number and assign the treatment group without revealing allocation to study staff. Study personnel will input this code into the tDCS device, which will control whether the participant receives active or sham stimulation. Only the participant number will be visible to study staff; treatment allocation will remain concealed.

To preserve the double-blind study design, all investigators, site staff, and participants will remain blinded to treatment assignment throughout the study. An independent statistician at the University of South Carolina (USC) will manage treatment codes using a coded device system provided by Soterix Medical. Each participant will be assigned a unique device code corresponding to their stimulation condition, which will remain consistent for all sessions. Each tDCS device provided by Soterix will come with codes pre-programmed on the device, and only the unblinded member will know the value of the codes. The speech-language pathologist responsible for baseline assessments, treatment delivery, and post-treatment assessments will remain blinded to group allocation.

Potential unblinding due to stimulation-related sensations (e.g., tingling or skin irritation) will be mitigated through the use of sham stimulation protocols designed to mimic active tDCS sensations. Endpoint assessments will be completed and scored by staff blinded to group assignment to further minimize detection bias. In the event of a serious adverse event (SAE) or medical emergency, unblinding may occur for an individual participant if deemed necessary for clinical decision-making. Unblinding will be conducted only by authorized personnel and must be reported to the principal investigator and Data and Safety Monitoring Board (DSMB). Inadvertent unblinding, if it occurs, will also be documented and reported.

Efforts will be made to ensure the tDCS devices and sham settings are indistinguishable in appearance and function. All data collection and outcome assessments will be conducted under strict protocols to maintain blinding integrity and minimize potential sources of bias.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the intervention will be monitored through standardized documentation, including mandatory participant report forms, treatment logs, and video recorded assessments, which serve as source documents for compliance evaluation. The lead SLP will oversee treatment fidelity and ensure data accuracy in coordination with the Data Core Unit.

The lead SLP will train site personnel per SOPs, with initial review of all assessments and subsequent random review of 10% of assessments. Treatment fidelity will be evaluated by direct observation via teleconference or in-person of the first participant at each site and random review of 10% of sessions via a HIPAA-compliant videoconferencing system. Some assessments, as described in Table 2, will be video recorded and scored offline; the Philadelphia Naming Test will be scored by blinded raters, with oversight

by the lead SLP, who will remain blinded to treatment allocation. Monthly meetings between the lead SLP and study SLPs will ensure protocol adherence, uniformity of procedures, and resolution of discrepancies.

6.5 CONCOMITANT SPEECH THERAPY

Participants with aphasia diagnosis that are currently receiving formal speech and language therapy will be required to temporarily discontinue involvement until study completion. Participants will also be asked not to initiate any new participation in aphasia support groups at the time of study enrollment.

6.5.1 RESCUE MEDICINE

This section is not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

This is an intent-to-treat study. Discontinuation from tDCS does not mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE) and each site will document AEs in the AE log.

A comprehensive description of **Standard Procedures for Adverse Event Screening and Monitoring** is provided in the Safety Monitoring SOP.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. If the participant withdraws from the study voluntarily, the PI will be notified and the withdrawal status will be appropriately documented in the participant's record, per IRB regulations. The participant will be asked to participate in an Early Study Termination Visit prior to discontinuing the study. This visit will be offered in a virtual format as needed.

If a participant is no longer able to receive tDCS stimulation for any reason, tDCS will be discontinued but the participant will continue to be followed for outcomes. If the participant reports a change in health status or any Adverse Event that may preclude tDCS, the PI will be consulted and will make a determination if the participant can continue with the study intervention. Any missed visits will be recorded in the participants research record, including the reason for the missed visit. If a participant chooses not to withdraw and still has missed appointments, we will continue the intervention until the planned duration while recording the number of missed appointments. We will utilize the number of missed appointments for statistical analysis.

7.3 LOST TO FOLLOW-UP

Every possible effort will be made to contact participants for all study visits, including follow-up visits. If a participant misses one or more treatment sessions for any reason, the study staff will complete as many sessions with that participant as possible within the 21-day treatment window. The study team will attempt to contact each participant for each follow up visit. Should a participant continue to be unreachable at the time of the final follow up visit, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

A large number of our participants have already participated in previous aphasia studies and know that new studies will likely be available to them in the future; therefore, we typically get a small group of people that are lost to follow-up. All sites are also active in the local community, hosting events and support groups to advocate for those with aphasia. This is also beneficial and reduces the number of those lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Assessment administration
See Section 1.3 above for a description of assessment administration. Please refer to STARS Clinical Reference Guide for severity & interpretation scales for each assessment.

Psychometric properties of Primary Outcome Measure
The primary measure (Philadelphia Naming Test) has been shown in clinical and research use to be moderately to highly reliable. The Aphasia lab has used this measure in past studies and has put in place scoring procedures to reduce variability in scoring including a mentor program so that new raters always have adequate support and the same training procedures. All students complete a video recording training, guided practice, and feedback on all initial rating attempts. In addition to this initial training, new raters (first-year graduate students) are paired with experienced raters (second-year graduate students) who are second raters on all initial scoring assignments. All raters have access to Sara Sayers and to experts in the transcription and coding of naming (Dr. Grant Walker) to answer questions that cannot be answered by their peers. Inter- and intra-reliability measures will be collected and analyzed for 10% of assignments scored once a year.

The PNT has seen extensive use in the development and testing of theoretical models of naming, particularly the interactive two-step model[53, 54], implying strong construct validity based on its fit with lexical access theory[1]. PNT accuracy scores correlate with global measures of aphasia severity, while showing weak correlations with demographic variables such as age and education—this supports both its content and criterion-related validity: it measures what it should measure (naming deficits) and does so relatively independently of irrelevant demographic factors[55].

Description of Screening, Baseline, and Follow-Up Assessments

1. Optional virtual pre-screening. Prior to initiating any study-related screening activities, potential participants will be offered the opportunity to learn more about the study through a virtual pre-screening process that will also help minimize travel burden and screen failures. No identifiable information beyond what is necessary for eligibility assessment will be collected at this stage.

2. Obtain written informed consent and complete the case history questionnaire/MRI safety screening/tDCS safety screening.

3. Structural neuroimaging scans collected at screening only.
   Collect the following MRI scans: T1, T2 and DTI.
   Administration time is approximately 30-45 minutes.

4. Administer the *Western Aphasia Battery-Revised* (WAB-R)[2]
   *Secondary Outcome Measure – collected at screening and visits 17, 18, and 19
   The WAB-R will characterize a participant's overall language impairment through the evaluation of the main clinical aspects of language functioning, including speech content, speech fluency, auditory comprehension, repetition, naming, and reading. The WAB-R allows for the differentiation of these specific language abilities, as well as the classification of aphasia type. The WAB-R also yields a composite score, the Aphasia Quotient, which provides an overall measure of severity, in which lower scores denote more severe aphasia[2]. Speech-language pathologists (SLPs) will refer to the WAB-R manual and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures. SLPs and central raters will score the initial WAB-R. Central raters will score all post treatment WAB-R assessments.
   Administration time will range between 30-60 minutes.

5. Administer the *Philadelphia Naming Test* (PNT)[1]
   *Primary Outcome Measure – collected at each assessment visit (once per day over 2 consecutive visits at each time point; during screening the PNT is administered once for eligibility and a second time at the baseline evaluation)
   The PNT is a picture-naming task consisting of 175 high- and medium-frequency nouns that vary in length from 1-4 syllables. The participant has up to 30 seconds to name each picture. SLPs will refer to the PNT manual for correct naming and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
   Administration time is approximately 20-60 minutes.

6. Administer the *Apraxia of Speech Rating Scale – Version 3.5* (ASRS 3.5)[8, 56]
   *Collected at baseline only
   The ASRS is used to rate the presence and severity of apraxia of speech (AOS). It quantifies the frequency and severity of the characteristics associated with AOS. SLPs will refer to Strand et al., 2014, Utianski et al., 2018, Duffy et al., 2023 and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
   Administration time is approximately 8-12 minutes.

7. Administer the *Wechsler Adult Intelligence Scale-3rd Edition, Matrix Reasoning Subtest* (WAIS-III)[9]
   *Collected at baseline only
   The WAIS-III Matrix Reasoning Subtest assesses nonverbal abstract problem solving and inductive reasoning. Participants are shown a series of patterns with one missing element and asked to identify the item from a field of 5 that completes the pattern. SLPs will refer to the WAIS-III manual and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
   Administration time is approximately 15 minutes.

8. Administer the *Pyramids and Palm Trees Test* (PPTT)[10]
   *Collected at baseline only

The PPTT is a test of semantic processing. This test assesses the degree to which a participant can access meaning from pictures and words. Information from the test will help determine whether a participant's difficulty in naming or pointing to a named picture is due to a difficulty in retrieving semantic information from pictures, or a difficulty in retrieving semantic information from words, or, in the case of a naming failure, a difficulty in retrieving the appropriate spoken form of the word (Howard & Patterson, 1992). SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
Administration time is approximately 10-20 minutes.

9. Administer the *Lexical Orthographic Familiarity Test* (LOFT)
   *Collected at baseline only
   The LOFT is a neuropsychological measure used to assess how familiar individuals are with the visual (orthographic) forms of words. It evaluates a person's ability to recognize real words based on their typical spelling patterns, without relying heavily on phonological processing. The LOFT is often used in research and clinical settings to study reading ability, acquired dyslexia, language disorders, and the distinction between lexical (word-based) and sub lexical (sound-based) reading processes. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
   Administration time is approximately 10-15 minutes.

10. Administer the *Charlson Comorbidity Index* (CCI)
    *Collected at baseline only
    The CCI includes cardiovascular, neurologic, pulmonary, renal, hepatic, metabolic, rheumatologic, malignant, and immunologic conditions. Certain conditions, such as metastatic malignancy and AIDS, carry higher weights due to their stronger association with mortality. The optional age adjustment will be applied, adding 1 point for each decade over 50 years of age, to improve prognostic accuracy in older populations. While the CCI provides a standardized measure of comorbidity burden, it is used as a supplement to clinical judgment rather than a stand-alone decision-making tool. Predicted mortality associated with a given score varies by population, setting, and follow-up period. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding scoring procedures.
    Administration time is approximately 5-10 minutes based on chart review and verification of information from participant and/or care partner.

11. Administer the *Stroke and Aphasia Depression Questionnaire-10* (SADQ-10)
    *Collected at baseline only
    The SADQ-10 is a brief observational screening tool completed by the care partner used to detect symptoms of depression in people who have had a stroke, particularly those with aphasia who may be unable to communicate their emotional state verbally. It consists of 10 items based on the participant's recent behavior (e.g., tearfulness, social withdrawal, irritability). Higher scores indicate a greater likelihood of depression. The SADQ-10 is valued for being easy to administer and suitable for individuals with communication impairments. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is approximately 5 minutes.

12. Administer the *NIH Stroke Scale* (NIHSS)
    *Collected at baseline only, and throughout study only as indicated by clinician judgement
    The NIHSS is a standardized clinical assessment tool used to measure the severity of neurological impairment caused by a stroke. It evaluates key functions such as level of consciousness, vision, motor strength, sensation, coordination, language, and speech. Scores range from 0 to 42, with

higher scores indicating more severe deficits. The NIHSS is widely used in emergency settings to guide treatment decisions, monitor neurological status over time, and standardize stroke severity reporting in research. SLPs will refer to the NIHSS guidelines and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
Administration time is approximately 5-10 minutes.

13. Administer the *NRS-FRS Fatigue Scale*
    *Collected at baseline and visits 17, 18, and 19
    The NRS-FRS Fatigue Scale is a single item assessment of self-perceived fatigue specifically for individuals' post-stroke. It consists of statements explaining fatigue and asking participants to rate their agreement on a Likert scale. Higher scores indicate more severe fatigue. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is approximately 5 minutes.

14. Administer *Concomitant Speech Therapy Questionnaire*
    *Collected at screening and visits 17, 18, and 19
    This brief adapted questionnaire will be used to verify status of involvement with any formal speech-language pathology intervention. SLPs will refer to STARS Clinical Reference Guide for explicit instructions regarding administration.
    Administration time is 3-5 minutes.

15. Administer the *Stroke and Aphasia Quality of Life Scale-39* (SAQOL-39)[5]
    *Secondary Outcome Measure – collected at baseline and visits 17, 18, and 19
    The SAQOL-39 is a quality-of-life assessment specific to the stroke population with aphasia. It contains 39 items relevant to quality of life that the participant rates from a scale of 1-5 (1=definitely yes, 2=mostly yes, 3=not sure, 4=mostly no, 5=definitely no). When scored it provides a mean score and breaks down items into three different domains: physical score, communication score, and psychosocial score. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is approximately 15-20 minutes.

16. Administer the *Communicative Activities of Daily Living- Third Edition* (CADL-3)[3]
    *Secondary Outcome Measure – collected at baseline and visits 17, 18, and 19
    The CADL-3 is a standardized assessment used to evaluate functional communication abilities by simulating real-life situations, assessing how well a person communicates in daily contexts: social interactions, reading/writing/using numbers, contextual communication and nonverbal communication. SLPs will refer to the CADL-3 manual and STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is approximately 30-45 minutes.

17. Administer the *Communicative Effectiveness Index* (CETI)[4]
    *Secondary Outcome Measure – collected at baseline and visits 17, 18, and 19
    The CETI is a 16-item questionnaire that consists of everyday communication situations, including verbal and non-verbal skills, to assess functional communication skills in adults with aphasia. Caregivers rate the person's communication effectiveness using a 100-point visual analog scale, with higher scores indicating better functional communication. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is 5-10 minutes.

18. Administer the *Communication Confidence Rating Scale for Aphasia* (CCRSA)[6, 7]
    *Secondary Outcome Measure – collected at baseline and visits 17, 18, and 19
    The CCRSA consists of a short series of confidence ratings about how confident they feel in 10 communication situations. The participant indicates on a scale from 1-5 how confident they feel in the specified situation. Higher scores indicate more positive responses, and a greater feeling of confidence. SLPs will refer to the STARS Clinical Reference Guide for explicit instructions regarding administration and scoring procedures.
    Administration time is approximately 5-10 minutes.

19. Administer *Discourse Measures*
    *Secondary Outcome Measure – collected at baseline and visits 17, 18, and 19
    a. Procedural discourse tasks administered: 1) PB&J and 2) Scrambled Eggs
    b. Narrative discourse tasks administered: 1) Cinderella and 2) Little Red Riding Hood
    SLPs will refer to STARS Clinical Reference Guide for explicit instructions regarding administration.

8.2 SAFETY AND OTHER ASSESSMENTS

At each treatment visit (Visits 2-16), staff will perform standardized safety evaluations including pre- and post-session physiological measurements (vital signs), a symptom questionnaire, an assessment of adverse events, visual inspection of the electrode sites, and a pre- and post-session Wong-Baker FACES pain rating questionnaire. At the baseline visit and 1-week post treatment, 4-weeks post treatment, and 24 weeks post treatment, staff will perform standardized safety evaluations including a symptom questionnaire and an assessment of adverse events. All findings and any adverse events will be documented in the participant's source record and entered into REDCap. Abnormal vital signs or concerning symptoms trigger pre-specified repeat measures and, if persistent, escalation to the study physician and termination of the visit when indicated. SLPs will refer to the STARS Safety Monitoring SOP for explicit instructions regarding repeat measures and escalation procedures. AEs and SAEs will be graded for severity and assessed for expectedness and relatedness; SAEs will be reported to NIDCD, the IRB and the DSMB per the timelines in Safety Monitoring SOP.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse Event (AE): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (laboratory finding, symptom, or disease), temporally associated with participation in the research, whether or not considered related to the subject's participation.

Unexpected Adverse Event: Any AE whose specificity or severity is not consistent with the risk information described in the protocol, Investigator Brochure (if applicable), informed consent document, or other study documentation; or not consistent with what is known in general about the condition being studied.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Event (SAE): Any AE that meets one or more of the following criteria:
1. Results in death.
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred).

3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in a persistent or significant disability/incapacity.
5. Results in a congenital anomaly or birth defect.
6. Any other AE that, based on appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the above outcomes.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

All adverse events (AEs) and serious adverse events (SAEs) will be systematically collected in REDCap by each site and reported by the central site in compliance with NIDCD, NIH, and local site IRB requirements to ensure participant safety and regulatory oversight.

8.3.3.1 SEVERITY OF EVENT

Adverse Events (AEs) will be graded according to their intensity:

- **Mild (Grade 1):** Transient or minimal symptoms; no limitation in daily activities; no medical intervention required.
- **Moderate (Grade 2):** Symptoms cause some limitation in daily activities; may require minimal medical intervention.
- **Severe (Grade 3):** Marked limitation in daily activities; requires significant medical intervention, hospitalization, or results in long-term consequences.
- **Potentially life-threatening (Grade 4)**
- **Death (Grade 5)**

Severity reflects the intensity of the event, not its relationship to the study treatment.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Each AE will be evaluated for its potential relationship to the study intervention. Events will be classified by the local study team, including PI and SLP (with input from review groups) as:

Adverse Event Attribution Categories:

1. **Unrelated**: The AE is clearly not related to the treatment
2. **Unlikely**: The AE is doubtfully related to the treatment
3. **Possibly**: The AE may be related to the treatment
4. **Probably**: The AE is likely related to the treatment
5. **Definitely**: The AE is clearly related to the treatment

Note: *for AEs that are categorized as Unrelated or Unlikely, brief detail supporting the attribution to an alternative cause of the AE should be provided.*

8.3.3.3 EXPECTEDNESS

An event is **unexpected** if it occurs in one or more subjects or others participating in a research protocol, and the event's nature, severity, or frequency is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in; (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document; and (b) other relevant sources of information, such as product labeling and package inserts; or
- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

The clinician in the study (Dr. Leo Bonilha) will be responsible for determining whether an adverse event (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 the study treatment.

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

Please refer to the Safety Monitoring SOP.

8.3.5 ADVERSE EVENT REPORTING

AE Reporting Summary Chart			
Event Type	***Initial Notification / Report***	***Timeline***	***Follow-Up / Detailed Report***
Death / Life-Threatening SAE	Verbal/email/phone by Study Coordinator/PI to NIDCD	Within 24 hours of awareness	Detailed written report within 7 business days
Other SAEs (non-life threatening)	Notification to NIDCD/ USC IRB as applicable	Within 7 business days of awareness	Written report within 15 business days
Unexpected AE (possibly/probably/ related/non-serious)	Written notification/ periodic report	Within 15 business days	Included in ongoing/annual reports
Expected AE (non-serious)	Not required for local site IRB	N/A	Included in periodic/annual reports
Unanticipated Problems / UPIRSOS	Report to USC IRB (or IRB of record) and NIDCD	No later than 10 business days after awareness	Detailed report including description, impact, corrective actions

All adverse events (AEs) and serious adverse events (SAEs) will be systematically collected, documented, and reported in compliance with NIDCD, NIH, and IRB requirements to ensure participant safety and regulatory oversight.

Collection Procedures

- AEs will be assessed at every study visit and during any unscheduled contact with participants; initially by the SLP at each site and, if needed based on severity, by the study physician.
- Central site (USC) will maintain a study-wide Adverse Event log to document participant number, description, onset, duration, severity, relatedness to the study treatment, action taken, outcome, expectedness, SAE, and investigator initials and date.
- Vital signs, standardized pain checklist, and direct participant/family report will be used to capture both anticipated and unexpected events.

Serious Adverse Events (SAEs)

- **Immediate Notification**
  - **Death or Life-Threatening Events:**
    The Program Manager or Principal Investigator (PI) must notify the **NIDCD Medical Officer within 24 hours** of receiving the information by telephone, fax, or email.

- **Follow-Up Written Reports**
  - **Death or Life-Threatening Events:**
    - **Within 7 business days:** Submit a detailed written report to:
      - NIDCD
      - Institutional Review Board (IRB)
      - All participating investigators
  - **Other SAEs (not death/life-threatening):**
    - Notify the NIDCD within **7 business days**.
    - Submit a detailed written report within **15 business days** to:
      - NIDCD
      - IRB
      - All participating investigators

Adverse Events (AEs)

- **Expected, Non-Serious AEs:**
  - Document in study records.
  - Summarize in periodic written reports to NIDCD, IRB, and participating investigators.
- **Unexpected, Non-Serious AEs:**
  - Notify study team at monthly meeting (within 30 business days).
  - Document in study records within 15 business days.
    - Documented in study records, study-wide AE reporting log, and summarized in periodic/annual reports to NIDCD, IRB, and investigators.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Please see section 8.3.5 for timelines and procedures for SAE reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

This section is not applicable.

8.3.8 EVENTS OF SPECIAL INTEREST

This section is not applicable.

8.3.9 REPORTING OF PREGNANCY

If a participant were to become pregnant during the intervention, we would discontinue the tDCS treatment but continue to follow the participant for the remainder of the study.

8.3.10 CLINICAL MANAGEMENT

This study will be conducted in compliance with the U.S. Department of Health and Human Services regulations for the protection of human subjects, as outlined in **45 CFR 46 (the Common Rule)**. All research activities will be reviewed and approved by an Institutional Review Board (IRB) prior to initiation.

The following adverse events guidance are for events possibly, probably, or definitely related to tDCS, which are rare but serious. All adverse events will be reported and documented according to AE/SAE reporting guidelines listed in this protocol (refer to section 8.3.5). The PI will be notified/consulted with for any AE categorized as Grade 3 or above. In case of any AE, study staff will manage symptoms, stabilize the participant, and contact local emergency services as appropriate. For greater detail, please see the Safety Monitoring SOP.

Adverse Event Example Severity Categorization					
Adverse Event	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially Life-Threatening)**	**Grade 5 (Death)**
Seizure	Brief seizure; no loss of consciousness. Note: study is discontinued.	Seizure with altered awareness. Note: study is discontinued.	Prolonged or recurrent seizures. Note: study is discontinued.	Status epilepticus or life-threatening seizure activity. Note: study is discontinued.	Death due to seizure. Note: study is discontinued.
Blood Pressure	Transient BP change; asymptomatic.	Symptomatic BP change requiring medical management.	Severe hypertension or hypotension requiring urgent intervention.	Life-threatening BP instability.	Death due to BP event.
Heart Rate	Mild tachycardia or bradycardia; asymptomatic.	Symptomatic heart rate abnormality; medical intervention indicated.	Severe arrhythmia requiring hospitalization.	Life-threatening arrhythmia requiring immediate intervention.	Death due to cardiac event.
Skin Sensitivity	Mild rash, itching, or sensitivity.	Moderate rash or discomfort.	Severe skin reaction, burning.	Life-threatening reaction.	Death due to skin reaction.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

Unanticipated Problem Involving Risks to Subjects or Others (UPIRSOS): An incident, experience, or outcome that meets ALL of the following:

1. Is **unexpected** (in terms of nature, severity, or frequency) given the procedures described in the protocol / investigator brochure / informed consent and what is known about the population.
2. Is **related or possibly related** to the subject's participation in the research.
3. Suggests that the research places subjects or others at a **greater risk of harm** than was previously known or recognized.

8.4.2 UNANTIPCATED PROBLEM REPORTING

Please refer to the Safety Monitoring SOP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

This section is not applicable.

9 STATISTICAL CONSIDERATIONS

The statistical considerations all refer to the Phase III portion of the trial. The key statistical details for the Phase II portion are described in section 9.4.6.

9.1 STATISTICAL HYPOTHESES

Primary Efficacy Endpoint(s):
The primary endpoint is the proportion of participants classified as "responders" on the Philadelphia Naming Test[1] (PNT), defined as a ≥ 9 point improvement in raw score at 4 weeks post-treatment. This is a superiority comparison of active tDCS + speech therapy vs sham tDCS + speech therapy. The null hypothesis (H_0) is that there is no difference in responder rates between groups. The alternative hypothesis (H_1) is that active tDCS results in a significantly higher responder rate.

- $\mathbf{H_0}$: $p_1 \leq p_0$ (where p_1 = responder rate in active tDCS group, p_0 = responder rate in sham group)
- $\mathbf{H_1}$: $p_1 > p_0$

Secondary Efficacy Endpoint(s):

- Change in PNT score (average score from two administrations over consecutive visits at each time point) from baseline to 4- week follow-up.
- Change in WAB-R Aphasia Quotient (AQ) from baseline to 4- week follow-up.
- Change in CADL-3 score from baseline to 4- week follow-up.
- Change in CETI score from baseline to 4- week follow-up.
- Change in SAQOL-39 score from baseline to 4- week follow-up.
- Change in CCRSA score from baseline to 4- week follow-up.
- The proportion of participants classified as "responders" on the PNT at 1- week follow-up.

- The proportion of participants classified as "responders" on the PNT at 24- week follow-up.
- The proportion of new AEs (safety).

These endpoints will also be analyzed as superiority comparisons between groups.

For each of the first six secondary endpoints, the null hypothesis (H_0) is that the group means are the same. The alternative hypothesis (H_1) is that the means are not equal between the active tDCS vs sham groups.

- **H_0**: $\mu_1 \leq \mu_0$ (where μ_1 = mean change in active tDCS group, μ_0 = mean change in sham group)
- **H_1**: $\mu_1 > \mu_0$

For the last three secondary endpoints, the null hypothesis (H_0) is that there is no difference in rates of each secondary outcome between groups. The alternative hypothesis (H_1) is that active tDCS results in a higher responder rate.

- **H_0**: $p_1 \leq p_0$ (where p_1 = responder rate in active tDCS group, p_0 = responder rate in sham group)
- **H_1**: $p_1 > p_0$

9.2 SAMPLE SIZE DETERMINATION

In our futility study[24, 42] we observed that 24% and 53% of participants with Broca's aphasia improved in the S-tDCS and A-tDCS groups, respectively, indicating that a good outcome with A-tDCS was 3.60 times the odds of a good outcome with S-tDCS. We will power this clinical trial to detect a more conservative but clinically important effect size. With N=49 per group, a one-sided alpha of 0.05, and assuming 24% of the participants in the S-tDCS group will be responders, a two group $\chi 2$ test will have 80% power to detect a significant difference (greater than or equal to 24%) between groups if the proportion of responders in the A-tDCS is at least 48%. The χ^2 calculation is conservative relative to the prespecified mixed model to be done in the final analysis. The final sample is inflated from n=98 to n=110 to account for up to 10% attrition. Phase II contributes the selected-dose and sham arms to the Phase III analysis pool.

9.3 POPULATIONS FOR ANALYSES

The analyses will be analyzed under the intent-to-treat principle (ITT). Under this principle, the evaluable sample will include all participants who are randomized.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

- Summary statistics of baseline variables will be compared by treatment groups. Dichotomous variables will be summarized as number (%). Percentages will be calculated based on the number of participants with available data for that variable. Continuous variables will be summarized by the mean and standard deviation (SD). Ordinal data will be presented as median (IQR).

- The primary efficacy endpoint will be tested using a one-sided p-value, and a 95% confidence interval will be reported for secondary and exploratory outcomes.
- Analyses will be adjusted for the covariates prespecified in sections 9.4.2 and 9.4.3.
- Assumptions of normality and homoscedasticity will be evaluated. Non-parametric alternatives or data transformations will be used when assumptions are violated.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary outcome is proportion of "responders" where "responder" is defined as a change in average number of pictures named on PNT assessment of 9 points or more from baseline to 4 weeks post treatment. At each time point, the PNT will be administered on two consecutive visits, and those two scores will be averaged.

The primary outcome, binary responder status, will be modeled using a repeated measures logistic mixed-effects model (SAS® GLIMMIX procedure with logit link and REPEATED subcommand). The model will include the following fixed effects: categorical visit (1 week and 4 weeks post treatment period) by treatment group (class variable) interaction, site, baseline PNT, baseline aphasia severity score, and age. We will assess error structures (compound symmetry, autoregressive, unstructured) based on the Akaike information criterion.

The primary hypothesis will be tested at a one-sided alpha of 0.05. We will estimate the odds ratio with a one-sided 95% confidence interval.

The primary analysis uses the ITT sample, which includes all participants who are randomized, and it will use a mixed-effects repeated measures model to account for participants with missing measurements; this is considered an implicit imputation approach if at least 1 post-baseline assessment is available. However, if baseline is the only assessment available, then we will impute missing data with multiple imputation by chained equations[57], assuming a monotone missing-at-random mechanism.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The analysis of the primary outcome will be tested at a one-sided 0.05 significance level. Secondary and exploratory analyses will be conducted regardless of the findings from the primary analysis and will not be corrected for multiple comparisons since these are supportive of the primary analyses and will be interpreted in this manner.

Outcomes:	**Scale Description:**	**Statistical Procedure:**
PNT	Continuous summary measure collected at screening, baseline and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, baseline PNT score, and age.

WAB-R AQ	Continuous summary measure collected at screening and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, and age.
CADL-3	Continuous summary measure collected at baseline and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, baseline CADL-3 score, and age.
CETI	Continuous summary measure collected at baseline and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, baseline CETI score, and age.
SAQOL-39	Continuous summary measure collected at baseline and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, baseline SAQOL-39 score, and age.
CCRSA	Continuous summary measure collected at baseline and 1 week, 4 weeks, and 24 weeks post treatment.	General linear mixed model of the change from baseline adjusted for categorical visit by treatment group (class variable) interaction, site, baseline WAB-R AQ score, baseline CCRSA score, and age.
Safety	The proportion of participants experiencing new AEs.	Chi-square or Fisher's exact test, as appropriate.

All secondary analyses will be conducted on the ITT sample. Missing data will be addressed as in the primary analysis. For each secondary outcome, we will present the adjusted means (LSMEANS) at 4 weeks post treatment with standard errors for each group.

9.4.4 SAFETY ANALYSES

The unblinded statistician at the Data Core Unit will produce semi-annual DSMB reports and at the request of the DSMB. The Closed Session DSMB reports will show tables by partially blinded treatment group. All serious adverse events will be summarized by "preferred term" and associated system-organ class and by treatment group in terms of frequency of the event and number of subjects having the event. For the DSMB report, severity and relatedness to the intervention will also be shown by treatment group as well as summary of the Wong-Baker FACES Pain rating scale[43].

At the end of the trial, the cumulative incidences of the specific SAEs related to treatment, as well as all SAEs, will be compared across groups.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Descriptive statistics (means, SDs, medians, proportions) will be used to summarize baseline characteristics by group. No inferential comparisons will be made to assess randomization success.

9.4.6 PLANNED INTERIM ANALYSIS

Enrollment will halt once 60 participants have been enrolled and completed Visit 18 (4-weeks post treatment). To decide whether to proceed from Phase II to Phase III, we will use stochastic curtailment based on the conditional power derived from the interim results of the primary endpoint analysis described above. The study will be stopped for futility (i.e. the Phase III trial will not be conducted) if the conditional power to reject the null hypothesis at the final analysis (assuming the alternative hypothesis is true) is below 20% for both active tDCS arms.

If conditional power for one active arm is less than 20%, that unpromising dose will be dropped, and Phase III will proceed with 1:1 randomization between the remaining active dose and sham. If the conditional power is greater than 20% for both the 1 mA and 2 mA arms, the effect size between the two active doses will be estimated using Cohen's h. If the difference is small (Cohen's $h<0.2$), Phase III will proceed with the 1 mA dose, as there is no justification for using the higher dose. If there is a meaningful difference (i.e. Cohen's $h > 0.2$), Phase III will randomize participants 1:1 to the 2mA dose or sham.

In consultation with the NIDCD, we may re-estimate the sample size based on the interim analysis and proceed as appropriate for Phase III.

This trial will include two statistical teams. One at USC (Dr. Hardin) and one at MUSC (Dr. Cassarly). The statistical team at USC will be unblinded, while the MUSC team will remain blinded. The unblinded statistician will perform the statistical analyses, and they will be presented at the unblinded sessions at the DSMB.

Blinding will be ensured by maintaining separate roles for the blinded and unblinded statistical teams throughout the trial. The unblinded statistician at USC will have access to treatment allocation information required for interim analysis and DSMB reporting, while the MUSC statistical team will remain blinded to treatment assignments for the duration of the trial, including during data cleaning, preparation of analysis datasets, and final analyses. Randomization data will be stored securely with access restricted to the unblinded statistician and designated unblinded personnel. Interim safety and efficacy data will be reviewed only during closed DSMB sessions, with no treatment-specific results shared with the investigative team or the blinded statistician. The data management system (REDCap) will maintain treatment allocation in a masked field to protect the blind during data handling. Blinding

will be maintained until the database is locked and the analysis plan has been finalized and signed, at which point the blind will be broken for the final analysis.

9.4.7 SUB-GROUP ANALYSES

Subgroup analyses will be conducted on primary and secondary outcomes by:

- Age group
- Sex
- Aphasia severity (WAB-AQ strata)

The primary analysis model will be repeated with a main effect for subgroup and a subgroup*treatment group interaction term. Results will be interpreted cautiously and considered exploratory.

Sex as a Biological Variable. We have not detected significant sex-related differences in outcomes in the prior tDCS Phase II futility study[24]. Nonetheless, we plan to perform sub-group analyses to evaluate sex as a biological variable and determine whether sex is associated with tDCS and treatment outcomes.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant-level data will not be tabulated; only summary statistics and aggregated results will be provided.

9.4.9 EXPLORATORY ANALYSES

Various discourse lexical and syntax variables on narrative tasks at the 4-week post-treatment timepoint compared to baseline will be analyzed using the approach described in section 9.4.3. These analyses are hypothesis-generating and will be interpreted accordingly.

If, after the interim analysis, the study proceeds into Phase III and the Cohen's h in Phase II was <0.2, a sensitivity analysis comparing the combined tDCS doses versus sham will be made using the same approach described in section 9.4.2.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to completing study assessments or interventions.

The informed consent template approved by USC IRB will be used by subsites with local context added.

Optional Virtual Pre-Screening
In an effort to reduce cost and travel burden on potential participants, we will implement an optional pre-screen process to minimize screen failures. The pre-screening will include a verbal consent process and study description, and may include: review of medical history, case history information, MRI screening or review of past clinical MRI scan, and the bedside WAB. This step ensures that individuals are adequately informed about the purpose of pre-screening, the type of information that will be collected, and how their data will be used to determine eligibility. The virtual pre-screening will be presented in clear, accessible language and will require participants to acknowledge their understanding and voluntary agreement before proceeding. No identifiable information beyond what is necessary for eligibility assessment will be collected at this stage. Completion of the virtual pre-screening does not constitute full study enrollment; individuals who meet preliminary eligibility criteria will be invited to participate in the in-person screening and written informed consent process prior to enrollment. A pre-screening log will be kept at each site to document enrollment efforts.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., legally authorized representative), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian, and this fact will be documented in the participant's record. For sites requiring HIPAA forms, participants will complete them to ensure compliance with institutional privacy policies. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Individuals who sign the consent form and participate in the formal screening process and fail to meet eligibility will be reported as screen failures.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants and investigator. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and 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.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. 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 sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), or regulatory agencies 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, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data Coordinating Unit at USC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Data Coordinating Unit at USC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Data Coordinating Unit at USC.

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g., legal authorized representative) this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian, and this fact will be documented in the participant's record. For sites requiring HIPAA forms, participants will complete them to ensure compliance with institutional privacy policies.

Participation in this study should not put participants in any legal risk, even in the case of a breach of confidentiality. We will undertake every effort to keep the information in the study confidential. Participants will be assigned a code number in order to keep the information confidential. The networks on which the information will be stored are password protected. Everybody involved in the study will have completed the appropriate training and are fully aware of confidentiality issues. No names will be included in any publications resulting from this work

Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

See Data Management and Sharing Plan for a comprehensive review of the data storage and use plan.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator/Medical Monitor
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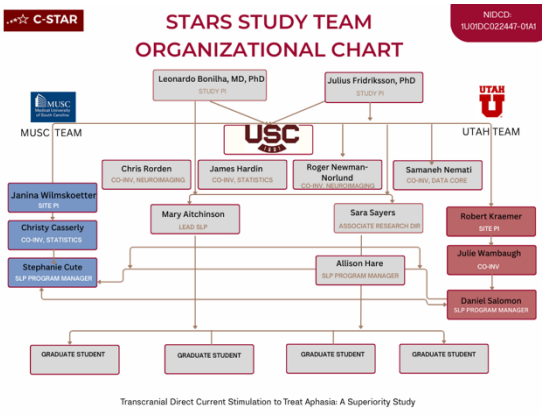

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including stroke recovery, brain stimulation, statistics, and language and aphasia. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least annually to evaluate the progress of the trial as well as assess safety and efficacy data on each arm of the study including the interim analysis. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the NIDCD.

10.1.7 CLINICAL MONITORING

The study will have an independent clinical trial monitor from USC. Clinical site monitoring will be 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 is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by an independent clinical trial monitor from USC.
- On-site or virtual centralized monitoring will be done yearly with random sampling and expanded sampling if needed.
- The PI and the study team will be provided copies of monitoring reports within 21 days of visit.
- The PI and the study team will routinely review safety trends during monthly team meetings.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The lead SLP and Program Manager will perform regular reviews of study materials to ensure compliance with regulatory requirements and ethical standards. To ensure data integrity and accuracy, the lead SLP will train study personnel at each site on Standard Operating Procedures (SOPs) which will be clearly stated in the STARS Clinical Reference Guide. They will periodically review workflows to prevent systematic biases or errors. Fidelity in behavioral assessments and treatment is a core aspect of this study. We also plan to publish the clinical trial design and SOPs, as this provides a comprehensive summary of the protocol and may be of use to the research community for planning other trials. We have successfully adopted this strategy in the past[58].

The lead SLP will train study personnel and local SLPs to ensure that assessments and speech therapy procedures outlined in the SOPs are meticulously followed. This adherence translates to consistent application across participants, ensuring uniformity in data collection. SLPs will be required to maintain the integrity of the therapeutic model by following the prescribed duration, frequency, and techniques of treatment sessions. The lead SLP will conduct periodical reviews of the assessments to ensure proper conduct.

The Lead SLP will review 10% of all assessments across all sites for fidelity with assessment administration and scoring. Monthly study-team fidelity meetings ensure the intervention is delivered as intended, detect drift, identify training needs, and document corrective actions so trial integrity is preserved.

The lead SLP will also continuously monitor scoring of the Philadelphia Naming Test performed by master's students in speech-language pathology who are blinded to treatment arms. It should be emphasized that the lead SLP will also remain blinded to randomization and treatment allocation. The lead SLP will meet on a regular basis with the SLPs involved in the study to review and guide procedures, documentation, and ensure uniformity in data collection.

The Program Manager will be responsible for ensuring that the demographic, clinical, and neuroimaging data obtained in this study is organized, clearly identified, and made available following the DSMB meetings.

MRI scans and video recordings of assessment will be stored in an institutionally approved secure storage platform, Dropbox. All behavioral datapoints will be stored in REDCap.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Please refer to the Data Management and Sharing Plan.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 10 years. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

For further information, please refer to the Data Management and Sharing Plan.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to NIDCD Program Official and USC Data Coordinating Unit. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Publication of the results of this trial will be governed by the policies and procedures developed by the Center for the Study of Aphasia Recovery (C-STAR).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDCD has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
AQ	Aphasia Quotient
A-tDCS	Active Transcranial Direct Current Stimulation
CADL-3	Communication Activities of Daily Living- Third Edition
CCRSA	Communication Confidence Rating Scale for Aphasia
CETI	Communication Effectiveness Index
CFR	Code of Federal Regulations
CHAT	Codes for the Human Analysis of Transcripts
CLAN	Computerized Language Analysis
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
C-STAR	Center for the Study of Aphasia Recovery
DMU	Data Management Unit
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EEG	Electroencephalography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LOFT	Lexical Orthographic Familiarity Test
LSMEANS	Least-squares Means
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MUSC	Medical University of South Carolina
NCT	National Clinical Trial
NIH	National Institutes of Health
NIDCD	National Institute on Deafness and Other Communication Disorders
OHRP	Office for Human Research Protections
PI	Principal Investigator
PNT	Philadelphia Naming Test
PPTT	Pyramids and Palm Trees Test
QA	Quality Assurance

QC	Quality Control
SADQ-10	Stroke Aphasia Depression Questionnaire
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAQOL-39	Stroke and Aphasia Quality of Life Scale
SLP	Speech-Language Pathologist
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SpARc	Speech Entrainment for Aphasia Recovery
S-tDCS	Sham Transcranial Direct Current Stimulation
STARS	Superiority Trial of Aphasia-focused Rehabilitation with tDCS Stimulation
tDCS	Transcranial Direct Current Stimulation
UofU	University of Utah
UP	Unanticipated Problem
US	United States
USC	University of South Carolina
VPM	Verbs Per Minute
WAB-R	Western Aphasia Battery- Revised
WAIS-III	Wechsler Adult Intelligence Scale III
WPM	Words Per Minute

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1	10/01/25	IRB approved version 1	To be reviewed by NIDCD
1.1	12/18/25	Revisions re: NIDCD feedback	To be reviewed by NIDCD
1.2	02/03/26	Revisions re: NIDCD feedback	To be reviewed by NIDCD
1.3	02/26/26	Revisions re: NIDCD feedback	To be reviewed by NIDCD
2.0	03/02/26	Revisions to be submitted to IRB	To be reviewed by IRB
3.0	05/27/26	Revisions to be submitted to IRB	To be reviewed by IRB
4.0	06/16/26	Changed length of computerized lexical semantic therapy task to 45 minutes, beginning at the same time as tDCS stimulation; added possibility of in-home study activities.	To remain consistent with previous tDCS trial.

11 REFERENCES

1. Roach A, Schwartz MF, Martin N, Grewal RS, Brecher A. The Philadelphia Naming Test: scoring and rationale. Clin Aphasiol. 1996;24:121–133.
2. Kertesz A. The Western Aphasia Battery – Revised. New York: Grune & Stratton; 2007.
3. Holland AL. Communication Activities of Daily Living – Third Edition (CADL-3). Torrance, CA: Western Psychological Services; 2018.
4. Lomas J, Pickard L, Bester S, Elbard H, Finlayson A, Zoghaib C. The communicative effectiveness index: development and psychometric evaluation of a functional communication measure for adult aphasia. J Speech Hear Disord. 1989;54:113–124.
5. Hilari K, Byng S, Lamping DL, Smith SC. Stroke and Aphasia Quality of Life Scale-39 (SAQOL-39): evaluation of acceptability, reliability, and validity. Stroke. 2003;34:1944–1950.
6. Babbitt EM, Heinemann AW, Semik P, Cherney LR. Psychometric properties of the Communication Confidence Rating Scale for Aphasia (CCRSA): phase 2. Aphasiology. 2011;25:727–735.
7. Cherney LR, Babbitt EM, Semik P, Heinemann AW. Psychometric properties of the Communication Confidence Rating Scale for Aphasia (CCRSA): phase 1. Top Stroke Rehabil. 2011;18:352–360.
8. Strand EA, Duffy JR, Clark HM, Josephs K. The Apraxia of Speech Rating Scale: a tool for diagnosis and description of apraxia of speech. J Commun Disord. 2014;51:43–50.
9. Kaufman AS, Lichtenberger EO. Assessing Adolescent and Adult Intelligence, 3rd ed. Hoboken, NJ: Wiley; 2006.
10. Howard D, Patterson K. The Pyramids and Palm Trees Test: A Test of Semantic Access from Words and Pictures. London: Harcourt Assessment; 1992.
11. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373–383.
12. Leritz EC, McGlinchey RE, Lundgren K, Grande LJ, Milberg WP. Using lexical familiarity judgments to assess verbally mediated intelligence in aphasia. Neuropsychology. 2008;22:687–696.
13. Chapple CM, Preece MR, Doesborg P, et al. The Stroke Aphasia Depression Questionnaire (SADQ-10): validation of a 10-item instrument. Clin Rehabil. 2004;18:191–195.
14. Engelter ST, Gostynski M, Papa S, et al. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. Stroke. 2006;37:1379–1384.
15. Gronberg A, Henriksson I, Stenman M, Lindgren AG. Incidence of aphasia in ischemic stroke. Neuroepidemiology. 2022.
16. Kauhanen ML, Korpelainen JT, Hiltunen P, et al. Aphasia, depression, and non-verbal cognitive impairment in ischemic stroke. Cerebrovascular Diseases 2000;10:455–461.
17. Code C, Hemsley G, Herrmann M. The emotional impact of aphasia. Seminars in speech and language 1999;20:19–31.
18. Hilari K, Byng S. Health-related quality of life in people with severe aphasia. Int J Lang Commun Disord 2009;44:193–205.
19. Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev. 2016;CD000425.
20. Kiran S, Meier EL, Johnson JP. Neuroplasticity in aphasia: A proposed framework of language recovery. J Speech Lang Hear Res. 2019;62:3973–3985.
21. Lorga M, Higgins J, Caplan D, et al. Predicting language recovery in post-stroke aphasia using behavior and functional MRI. Sci Rep. 2021;11:8419.
22. Varkanitsa M, Kiran S. Understanding, facilitating and predicting aphasia recovery after rehabilitation. Int J Speech Lang Pathol 2022.

23. Holland A, Fromm D, Forbes M, MacWhinney B. Long-term recovery in stroke accompanied by aphasia: a reconsideration. Aphasiology 2017;31:152–165.
24. Fridriksson J, Rorden C, Elm J, Sen S, George MS, Bonilha L. Transcranial direct current stimulation vs sham stimulation to treat aphasia after stroke: a randomized clinical trial. JAMA Neurol 2018.
25. Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 2011;118:40–50.
26. Kang EK, Kim YK, Sohn HM, Cohen LG, Paik NJ. Improved picture naming in aphasia patients treated with cathodal tDCS to inhibit the right Broca's homologue area. Restor Neurol Neurosci 2011;29:141–152.
27. Monti A, Cogiamanian F, Marceglia S, et al. Improved naming after transcranial direct current stimulation in aphasia. J Neurol Neurosurg Psychiatry 2008;79:451–453.
28. Shah PP, Szaflarski JP, Allendorfer J, Hamilton RH. Induction of neuroplasticity and recovery in post-stroke aphasia by non-invasive brain stimulation. Frontiers in Human Neuroscience 2013;7:888.
29. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia in adults with aphasia after stroke. Cochrane Database Syst Rev 2019;5:CD009760.
30. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine—new approaches and challenges. Acta Inform Med 2008;16:219–225.
31. Fridriksson J, Baker JM, Whiteside J, et al. Treating visual speech perception to improve speech production in nonfluent aphasia. Stroke 2009;40:853–858.
32. Charvet LE, Shaw MT, Bikson M, Woods AJ, Knotkova H. Supervised transcranial direct current stimulation (tDCS) at home: a guide for clinical research and practice. Brain Stimul 2020;13:686–693.
33. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. J Affect Disord 2019;252:475–483.
34. Benussi A, Cantoni V, Manes M, et al. Motor and cognitive outcomes of cerebello-spinal stimulation in neurodegenerative ataxia. Brain 2021;144:2310–2321.
35. Pilloni G, Shaw M, Feinberg C, et al. Long-term at-home treatment with transcranial direct current stimulation (tDCS) improves symptoms of cerebellar ataxia: a case report. J Neuroeng Rehabil 2019;16:41.
36. Benussi A, Alberici A, Cotelli MS, et al. Cortico-spinal tDCS in ALS: a randomized, double-blind, sham-controlled trial. Brain Stimul 2019;12:1332–1334.
37. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke 2010;41:1229–1236.
38. Fridriksson J, Richardson JD, Baker JM, Rorden C. Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke 2011;42:819–821.
39. Iyer MB, Mattu U, Grafman J, Lomarev M, Sato S, Wassermann EM. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. Neurology 2005;64:872–875.
40. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain research bulletin 2007;72:208–214.
41. Nitsche MA, Niehaus L, Hoffmann KT, et al. MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. Clinical Neurophysiology 2004;115:2419–2423.
42. Bonilha L, Rorden C, Roth R, Sen S, George MS, Fridriksson J. Improved naming in patients with Broca's aphasia with tDCS. J Neurol Neurosurg Psychiatry 2023.
43. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988;14:9–17.

44. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. Cochrane Database of Systematic Reviews 2020.
45. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. Brain 2005;128:490–495.
46. Goldfarb R, Halpern H. Impairments of naming and word finding. The characteristics of aphasia. 1989:33–52.
47. Benson DF. Anomia in aphasia. Aphasiology 1988;2:229–235.
48. Fama ME, Lemonds E, Levinson G. The subjective experience of word-finding difficulties in people with aphasia: A thematic analysis of interview data. American Journal of Speech-Language Pathology 2022;31:3–11.
49. Best W, Greenwood A, Grassly J, Hickin J. Bridging the gap: can impairment-based therapy for anomia have an impact at the psychosocial level? International Journal of Language & Communication Disorders 2008;43:390–407.
50. Blanton S, Morris DM, Prettyman MG, et al. Lessons learned in participant recruitment and retention: the EXCITE trial. Phys Ther 2006;86:1520-1533.
51. Robinson KA, Dennison CR, Wayman DM, Pronovost PJ, Needham DM. Systematic review identifies number of strategies important for retaining study participants. J Clin Epidemiol 2007;60:757.e1-757.e19.
52. Shewan CM, Kertesz A. Reliability and validity characteristics of the Western Aphasia Battery (WAB). Journal of Speech and Hearing Disorders 1980;45(3):308-324.
53. Dell GS, Schwartz MF, Martin N, Saffran EM, Gagnon DA. Lexical access in aphasic and non-aphasic speakers. Psychological Review 1997;104:801-838.
54. Schwartz MF, Dell GS, Martin N, Gahl S, Sobel P. A case-series test of the interactive two-step model of lexical access: Evidence from picture naming. Journal of Memory and Language. 2006;54(2):228-264.
55. Walker GM, Schwartz MF. Short-form Philadelphia Naming Test: rationale and empirical evaluation. Am J Speech Lang Pathol 2012;21(2):S140–S153.
56. Utianski, RL, Duffy, JR, Clark, HM, Strand, EA, Botha, H, Schwarz, CG, Machulda, MM, Senjem, ML, Spychalla, AJ, Jack, CR Jr, Petersen, RC, Lowe, VJ, Whitwell, JL, Josephs, KA. Prosodic and phonetic subtypes of primary progressive apraxia of speech. Brain and Language 2018;184:54-65.
57. Rubin DB. Multiple imputation for nonresponse in surveys. Hoboken, NJ;: Wiley-Interscience, 2004.
58. Cassarly C, Doyle A, Ly T, Horn J, Aitchison M, Elm J, Fridriksson J, Bonilha L. Speech Entrainment for Aphasia Recovery (SpARc) phase II trial design. Contemp Clin Trials Commun 2021;24:100876.
59. Im S, Park GY, Kim TW, Lim SH. Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2024;45(7):3513-3516. doi:10.1007/s10072-024-07516-6.
60. Buchanan DM, Amare S, Gaumond G, D'Angiulli A, Robaey P. Journal of Clinical Medicine. 2023;12(13):4346. doi:10.3390/jcm12134346.
61. Bikson M, Grossman P, Thomas C, et al. Brain Stimulation. 2016 Sep-Oct;9(5):641-661. doi:10.1016/j.brs.2016.06.004.
62. Brunoni AR, Amadera J, Berbel B, et al. The International Journal of Neuropsychopharmacology. 2011;14(8):1133-45. doi:10.1017/S1461145710001690.
63. Burkhardt G, Kumpf U, Crispin A, et al.Lancet (London, England). Transcranial Direct Current Stimulation as an Additional Treatment to Selective Serotonin Reuptake Inhibitors in Adults With Major Depressive Disorder in Germany (DepressionDC): A Triple-Blind, Randomised, Sham-Controlled, Multicentre Trial. 2023;402(10401):545-554. doi:10.1016/S0140-6736(23)00640-2.

64. Borrione L, Cavendish BA, Aparicio LVM, et al. JAMA Psychiatry. Home-Use Transcranial Direct Current Stimulation for the Treatment of a Major Depressive Episode: A Randomized Clinical Trial. 2024;81(4):329-337. doi:10.1001/jamapsychiatry.2023.4948.
65. Roncero C, Mardigyan V, Service E, et al. Investigation Into the Effect of Transcranial Direct Current Stimulation on Cardiac Pacemakers. Brain Stimulation. 2020 Jan - Feb;13(1):89-95. doi:10.1016/j.brs.2019.08.010.