

**TRANSCRANIAL DIRECT CURRENT STIMULATION AND
APHASIA TREATMENT OUTCOMES**

NCT01686373

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Appendix I

Study protocol

1. SELECTION OF PATIENTS

Patients in this study will have chronic stroke-induced aphasia. Diagnostic evaluations will be conducted during the patients' initial visit to confirm aphasia diagnosis. Patients currently receiving speech and language treatment (apart from aphasia support groups) will be required to temporarily discontinue involvement until study completion.

1.1 Patient Inclusion Criteria

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

1. Patients must be willing and able to give informed consent.*
2. Patients must be willing and able to comply with study requirements.
3. Patients must be between 25- and 80-years of age.
4. Patients must be native English speakers.
5. Patients must be pre-morbidly right-handed.
6. Patients must have sustained a one-time ischemic stroke in the left-hemisphere.
7. Patients must be greater than 6-months post-stroke.
8. Patients must have an aphasia diagnosis as confirmed by the *Western Aphasia Battery-Revised*.
9. Patients must be MRI-compatible (e.g., no metal implants, not claustrophobic, etc.).
10. Patients must achieve at least 65% accuracy on naming task during screening.

1.2 Patient Exclusion Criteria

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

1. History of brain surgery
2. Seizures during the previous 12 months
3. Use of medications that lower the seizure threshold (e.g., Ritalin, Adderall, Bupropion, etc.)
4. Sensitive scalp (per patient report)
5. Able to overtly name more than an average of 140 out of 175 items during the pre-treatment picture naming test (Philadelphia Naming Test) during Visits 2 or 3
6. Unable to overtly name at least a total of 5 out of 160 items during the pre-treatment fMRI sessions during Visits 2 or 3

*The investigators in charge of this study are speech-language pathologists who have expertise in assessing, treating, consenting, and communicating with adults with speech-language impairment of many types and severities. It is important to note that aphasia is an impairment of speech-language, not intelligence, and that most often, in the absence of comorbid impairment(s), competence is not reduced but only masked by the speech-language impairment. The consent document is reviewed thoroughly, with verification questions asked frequently to ensure that the potential participant and his or her caregiver understand the scope of the research project. Only participants who clearly understand the research and are able to indicate consent to participate can be enrolled in this study. Caretakers, family, or friends must be present during consent approval, but they cannot consent for the participant. If written consent is not possible, they may act as witnesses for verbal consent. Crucially, because this population is not devoid of language and can make their wants, needs, and preferences known (either via impaired speech or via alternative communication modalities such as gestures, writing, etc.), participants who have the ability to consent also have the ability to inform the investigators that they wish to cease their participation if necessary.

2. STUDY PROCEDURES

2.1 Study Procedures Overview

After informed consent is received, a neurological examination will be performed and multiple screening assessments will be conducted including a tDCS and MRI safety screening (see below). If the patient passes the initial screening portion, speech and language diagnostic testing will be conducted during the same visit (Visit 1). During the next two visits (Visits 2 and 3), patients will undergo baseline assessments of naming ability and connected speech, and structural and functional MRI examinations. The fourth visit will include collection of blood sample, electrode positioning and tDCS treatment administration. Patients will receive 15 sessions (Visits 4-18) of tDCS treatment administration. At the beginning of Visit 4, eligible patients will be randomized to receive either A-tDCS (1 mA) or S-tDCS (placebo) for 15 consecutive weekdays (20-min per each 45-min behavioral treatment session). A computerized anomia treatment will be coupled with the stimulation. The computerized treatment task will be 45-minutes in total length, so that it will commence at the same time as the tDCS administration and continue for another 25-minutes after the tDCS has ceased. To assess cardiovascular arousal, blood pressure and heart rate will be measured before and after each session. Additionally, discomfort ratings will be recorded following the end of each session using the *Wong-Baker FACES Pain Rating Scale* and a weekly neurological exam will be administered by a neurologist. Utilizing a computerized picture naming assessment (which combines the 175 items from the PNT and 80 treated items) of trained and untrained nouns, all patients will be assessed at 8 different time points throughout the experiment: twice at baseline (Visit 2 and 3), twice immediately following the fifteenth (and final) treatment session (Visit 19 and Visit 20), twice at 4 weeks follow-up (Visit 21 and Visit 22), and twice at 6 months follow-up (Visit 23 and Visit 24).

2.2.1 Procedures for Screening (Visit 1)

The following procedures will be performed:

1. Obtain written informed consent:
 - A signed and dated informed consent form will be obtained from each patient before conducting any screening procedures. Patients will be then be assigned a temporary identification number for the purposes of initial screening.
 - All research staff authorized to obtain informed consent will have completed the Miami CITI course in the Responsible Conduct of Research and Protection of Human Subjects prior to their involvement with the study. Furthermore, they will be oriented to the study and trained by the study PI and study co-investigators who have all had extensive training and experience in the ethical and practical aspects of informed consent procedures.
2. Review inclusion/exclusion criteria
3. Obtain medical history
4. Conduct neurological examination
5. Administer the A-tDCS safety screening
6. Administer the MRI safety screening
7. Administer naming screen used to verify that patients comprehend task requirements

o Refer to computer setup for the treatment for information regarding the computerized naming assessment. A shortened naming screen (identical set up and response requirements) will be presented to patients. Patients will get three attempts to achieve at least 65% accuracy on the task. If a patient is unable to reach this level of accuracy, study enrollment will be discontinued.

2.2.2 Procedures for Diagnostic Testing (Visit 1)

If the patient passes the screening portion, diagnostic testing will be conducted during the same visit. The following diagnostic testing procedures will be performed:

1. Administer the *Western Aphasia Battery-Revised* (WAB-R):
 - o The WAB-R will characterize the patients' overall language impairment through the evaluation of the main clinical aspects of language functioning, including speech content, speech fluency, auditory comprehension, repetition, and naming. 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 (Kertesz, 2007). Speech-language pathologists (SLPs) will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 30-45 minutes.
2. Administer the *Boston Naming Test-Second Edition* (BNT):
 - o The BNT represents a measure of object naming abilities from a corpus of 60 line drawings. Object names are ranked along a continuum, with easier, more higher-frequency words appearing at the beginning of the test and more difficult, lower-frequency words appearing near the end. To eliminate patient frustration, the BNT implements a ceiling effect so that once the patient incorrectly names eight items in a row, testing will cease, with the assumption that (s)he would not correctly name the upcoming, more difficult words (Kaplan, Goodglass, & Weintraub, 2001). SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 5-20 minutes.
3. Administer Subtest 6 from the *Apraxia Battery for Adults-Second Edition* (ABA-2):
 - o Subtest 6 (Inventory of Articulation Characteristics) of the ABA-2 is a rating scale, in which speech characteristics are evaluated on 15 different items (e.g., the patient exhibits: marked difficulty initiating speech; highly inconsistent errors; or visible/audible searching). The range of scores on Subtest 6 is 0-15, where a score above 5 is thought to signify the presence of apraxia of speech, an impairment in the programming of movements for the purpose of speaking without neuromuscular deficit (Dabul, 2000). Higher scores indicate more severe apraxia of speech. SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-15 minutes.
4. Administer the *Pyramids and Palm Trees Test* (PPTT)
 - o The PPTT is a test of semantic processing. This test assesses the degree to which a patient can access meaning from pictures and words. Information from

the test will help determine whether a patient'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 manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 10-20 minutes.

5. Administer the *abstract reasoning sub-test of the WAIS*
 - This test is a measure of nonverbal reasoning. The WAIS sub-test was constructed to test whether individuals are able to reason by analogy and adopt this way of thinking as a consistent method of inference. SLPs will refer to the manual for explicit instructions regarding administration and scoring procedures. Administration time will range between 15-20 minutes.

2.2.3 Procedures for MRI Examination (Visits 2, 3)

The following procedures will be performed:

1. Run the patient on a 10-minute fMRI exam during visits two and three:
 - Instruct the patient to overtly name pictures representing nouns (n = 40) once they appear on the screen and to say nothing when abstract pictures (n= 20) appear on the screen
 - The pictures will be presented for 2 s each on a back-projected mirror located on top of the head coil
 - A non-ferrous microphone will be placed 1-3 cm from the patient's mouth and used to record naming attempts, which will be recorded with sufficient clarity for off-line scoring by a trained speech-language pathologist
2. Run the patient on high-resolution anatomical MRI scans during Visit 2:
 - Instruct the patient to do nothing during these scans

2.2.4 Procedures for the Computerized Naming Assessments (Visits 2, 3, 19-24)

The following procedures will be performed during Visits 2, 3, and 19-24:

1. Turn on the laptop computer and position in front of the patient
2. Set up and start internal web-camera for audio-visual recording.
3. Administer the combined *Philadelphia Naming Test* (PNT; Roach et al., 1996) on a laptop computer. *Note to clinician: The PNT (175 items) will also include 80 treated pictures for a total of 255 picture presentations:*
 - Instruct the patient to overtly name each picture as soon as it is displayed
 - Trials will end following a response or after 20-seconds have elapsed, in which the administrator will say the correct picture name in order to discourage perseveration on subsequent trials
4. Stop web-camera and save video file for later scoring of naming.

2.2.5 Procedures for the “Cinderella Story” picture discourse analysis (Visits 3, 19, 21, and 23)

The following procedures will be performed during Visits 3, 19, 21, and 23:

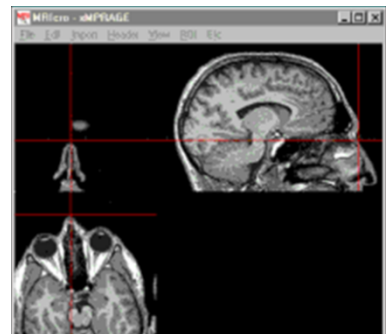
1. To be completed following the administration of the CNA-PNT, so the laptop computer and web-camera set-up will need to remain for this portion of the assessment
2. Place the picture book in front of the patient
3. Tell the patient, "I'm going to ask you to tell a story. Have you ever heard the story of Cinderella?" (Make note of answer) "Do you remember much about it? These pictures might remind you of how it goes. Take a look at the pictures and then I'll put the book away, and ask you to tell me the story in your own words." Allow the patient to look through the book (assist with page turning, if needed) and then, if necessary, prompt: "Now tell me as much of the story of Cinderella as you can. You can use any details you know about the story, as well as the pictures you just looked at." Continue until the patient concludes the story or it is clear s/he has finished.
4. Stop web-camera and save video file for later transcription

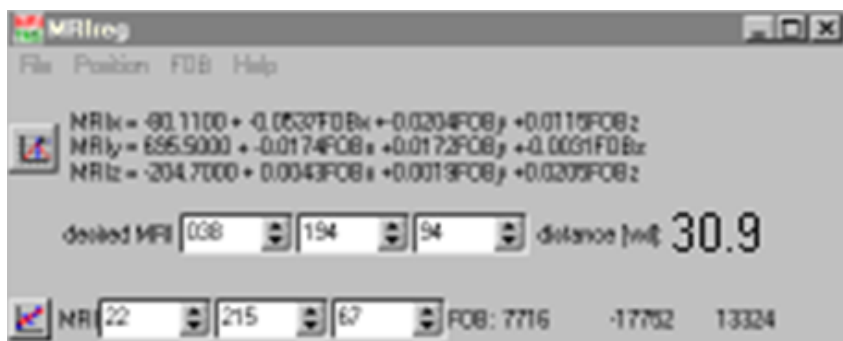
2.2.6 Procedures for Electrode Positioning (Visit 4)

The following procedures will be performed:

1. Fit the patient with a latex scalp cap and instruct them to sit as still as possible during this process
2. Identify and label the following six anatomical landmarks on the patient's scalp cap utilizing a permanent marker: 1) left ear; 2) right ear; 3) left eyebrow; 4) right eyebrow; 5) head apex; and 6) occipital bun
3. Upload the patient's anatomical T1 MRI scan (acquired from Visit 2) onto a computer utilizing *MRicro*, a computer program that allows for the viewing of MRI images.
4. Employing *MRicro*, select an anatomical location on the patient's T1 MRI scan (e.g., bridge of nose) by mouse-click
5. Move the magnet sensor from the *Flock of Birds* magnetic tracking system to the location on the patient's head which mirrors the anatomical position selected in *MRicro* from Step 4 and enter into the *MRireg* software, a computer program that registers a high-resolution MRI scan of the head with scalp locations
6. Repeat Steps 4 and 5 until the following five anatomical landmarks have been entered into *MRireg*: 1) left ear; 2) right ear; 3) bridge of nose; 4) head apex; and 5) occipital bun
7. Press the 'correlation line' button of *MRireg* after the five anatomical landmarks from Step 6 have been located
8. Enter the coordinates of the area of the left hemisphere with the highest level of activation within the peri-lesional area during correct naming on the fMRI naming task in the 'desired MRI' boxes (these coordinates will be identified by Dr. den Ouden and forwarded to you [SLP] on patient-by-patient basis)
9. *MRireg* will estimate the current distance of the magnet sensor wand from this point. Move the wand around the patient's head and once the most precise area is located, label the location on the patient's scalp cap with a star utilizing a permanent marker

Below: Example of Step 4





Left: Example of Steps 8 & 9. The 'desired MRI boxes' are displayed. Additionally, the current distance of the magnetic sensor from the coordinates entered in the 'desired MRI boxes' is displayed, which in this example, is 30.9 mm.

2.2.7 Procedures for Collection of Blood sample (Visit 4)

1. Collection of blood samples will be handled by the study coordinators (both are registered nurses) assisting Drs. Sen and Bachman
2. Once blood sample has been obtained, write patient number (as generated by the DCU) on the vial
3. Follow storage procedures as advised by Dr. Krupenko's lab at MUSC
4. At USC, place the blood sample in the lab freezer in Dr. Fridriksson's lab
5. At MUSC, place the blood sample in the designated lab freezer in Dr. Bachman's lab

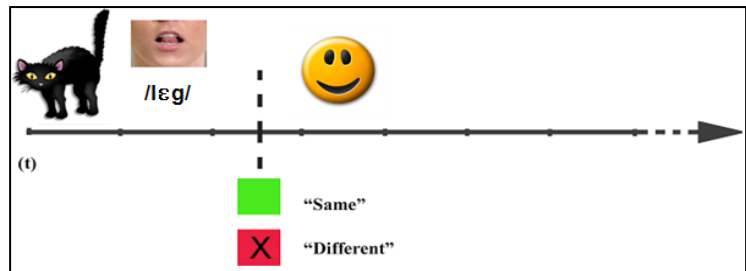
2.2.8 Procedures for Treatment (Visits 4-18)

The following procedures will be performed:

1. Measure and record the patient's blood pressure and heart rate
2. Carefully fit patients with their scalp cap (labeled from Visit 4)
3. Soak the 2 sponge electrodes in saline solution and place inside rubber electrode holders
4. Place the anode electrode under the designated area on the scalp cap that was located during the electrode positioning process (marked with a star during Visit 4). Remove the cap and secure electrode placement with a self-adhesive bandage
5. Place the reference cathode electrode on the patient's right orbito-frontal scalp (above the right eyebrow) and secure electrode placement with a self-adhesive bandage
6. Connect the electrode cables to the relay box positioned between the tDCS stimulator and the lap-top computer used to maintain experimenter and patient blinding. Start the software used for blinding (see an icon "tDCS+aphasia" on the desktop) and enter the patient number (obtained on the DCU web site) in the designated place. Make sure that the screen of the "blinding" lap-top is placed out of patients' sight.
7. Turn on tDCS stimulator
8. Set-up the computerized anomia task:
 - o Turn on computer and position in front of patient
 - o Plug in the red/green response buttons into the computer and position in front of patient
 - o Plug in the earbud headphones into the computer and place in patient's ears

- Play example sound clip to verify with patient that sound is sufficient; if sound is not sufficient, adjust volume until patient is satisfied
 - Locate the patient's designated treatment folder and open
9. Instruct the patient how to perform the self-administered computerized anomia treatment consisting of a picture-word matching task, which will be coupled with the stimulation
- The computerized treatment task will be 45-minutes in total length, so that it will commence at the same time as the tDCS administration
 - A picture will be presented for 2 s on a laptop computer screen and will be immediately followed by an audio-visual display of a male speaker's mouth saying a noun. Video of the speaker producing the noun is presented in synchrony with the audio via in-ear headphones. The spoken word either will or will not match the preceding picture. In the event of a match, instruct the patient to press a large green response button interfaced with the computer, and in the case of a non-match, instruct the patient to press a red button. Half of the picture/word pairs will match, while the other half will not. The computer will provide immediate visual feedback 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 patient's responses will be automatically saved, and the accuracy score from that session will be displayed on the computer screen.

Right: Example of the computerized treatment task. The picture representation for "cat" does not match the subsequent audio-visual presentation for "leg." Since the pair is not a match, the red button was correctly pressed, which lead to the immediate "smiley face" feedback.



10. "Click" on the START icon on the "blinding" computer to simultaneously start stimulation and the computer treatment task
11. Measure and record the patient's blood pressure and heart rate following treatment completion
12. Record any Adverse Events experienced during the treatment session or since the last visit on the AE log.
13. Assess and record the patient's comfort rating using the *Wong-Baker FACES Pain Rating Scale* following treatment completion



Left: A reproduction of the "Wong-Baker FACES Pain Rating Scale"

2.2.9 Procedures for Neurological Examination (Visits 8, 13, 18)

The following procedures will be performed:

1. All patients will be monitored closely for safety and neurological functioning during the duration of the study. In addition to the comfort ratings recorded daily the neurological examination administered during Visit 1 will be re-administered weekly by Drs. Sen or Bachman during the treatment phase.

2.2.10 Record medications for each patient.

A list of all current medications should be recorded in the appropriate location in WebDCU.

3. STATISTICAL CONSIDERATIONS FOR THE PRIMARY STUDY AIM

3.1 Analysis Sample

The primary analysis will be analyzed under the intent-to-treat principle (ITT). Under this principle, the evaluable sample will include all participants who are randomized regardless of the type of treatment that was actually administered. For the safety analyses, all randomized participants who receive at least one session of the treatment will be included, regardless of the duration of treatment administered.

3.2 Randomization and Blinding

The study is to be conducted in a double-blind manner. The subjects, the site investigators, and the USC and MUSC clinical staff involved in this study will not know the treatment assignment. Select members of the Statistical and Data Management Center will be partially blinded, i.e., they will know the treatment group assignment as A or B, but not whether the patient receives active tDCS or sham. The study statistician and the DSMB will have a sealed envelope with the treatment group identifiers. This envelope would only be opened if the study statistician is directed to open it by the DSMB or at the end of the futility study.

The randomization will take place centrally via the Trial Website. Subjects will be randomized 1:1 (A-tDCS: S-tDCS), controlling for clinical center, aphasia type, and severity (classified using the Western Aphasia Battery revised: WAB-R). The computer program developed at the DCU makes the treatment assignment based on the current status of treatment group distribution within each stratum as well as overall balance of treatment assignment. The randomization scheme will never be deterministic. The detailed randomization scheme and source codes will be provided in the Randomization Plan document.

A “Real-Time” randomization procedure is implemented via the Trial Website on the WebDCU™ System where the clinical center staff enters the basic baseline (e.g. aphasia type, and AQ severity) and eligibility information of a subject prior to enrollment. If the subject’s eligibility status is confirmed, the computer program on the WebDCU™ server will evaluate the treatment arm distribution and generate a patient number based on the randomization scheme. The SLP enrolling the patient will not see the treatment assignment, only a numeric patient number which is entered into a software package that controls whether the tDCS given is A-tDCS or S-tDCS. In order to mask treatment type (A-tDCS vs. S-tDCS) for both patients as well as the SLPs administering the treatment session (ie. setting up the tDCS and starting and monitoring the computerized treatment task), we use in-house software/hardware. As previously discussed, this setup allows for switching the tDCS on and off without any involvement from the patient or experimenter. The software is run on a lap-top computer connected to the tDCS stimulator. Treatment type is encoded in the software so that the administrator only needs to enter a patient and session number to start stimulation without knowing whether those specific numbers are

associated with A-tDCS or S-tDCS. The unblinded list of randomization codes and treatment assignments will be generated by the DCU and will be uploaded into the software by a software administrator who is not otherwise involved in the study.

3.3 Baseline Treatment Group Comparability

During the course of the study as a part of the DSMB reports, summary statistics for the following baseline variables will be computed and compared between treatment groups: age, gender, years of education, WAB-R, BNT-2, ABA-2, PPTT, and WAIS subtest. At study conclusion, the statistical tests for comparison will be two-sample t-test or Wilcoxon rank sum test for continuous scale variables and chi-square or exact test for categorical variables.

3.4 Primary Analysis

3.4.1 Primary Outcome

The primary outcome will be defined as the change in number of correctly named items on the PNT (pre-treatment and immediate post-testing). To assess change in naming ability, the primary outcome in this study, the PNT (plus a portion [N=80] of the trained items) will be administered twice (and averaged to reduce variability) on two consecutive days immediately before treatment starts and twice after treatment is completed. The change will be computed as the difference in the number of correctly named items comparing the average of the two pre-treatment PNT assessments to the average of the two post-treatment PNT sessions.

3.4.2 Statistical Hypotheses

The primary hypothesis is:

$$H_0: \mu_T - \mu_S \geq \delta$$

vs.

$$H_A: \mu_T - \mu_S < \delta$$

where μ_T is the expected change (pre-treatment and immediate post-testing) in the number of correctly named items for the treatment arm, μ_S is the expected change in the sham control group, and δ is the minimum improvement sufficient to warrant further evaluation of tDCS treatment. We define that minimum improvement to be 1.5 points more than the observed change in the sham control group. If we reject the null hypothesis, then tDCS is considered clearly ineffective (in improving anomia in stroke patients) and will not be considered for further study. If we fail to reject the null hypothesis, we would consider undertaking a Phase III study of tDCS.

3.4.3 Sample Size Determination

In preliminary studies, the mean difference in change from baseline in the active and sham groups in naming accuracy was ~2.5 points (Baker, Rorden, & Fridriksson, 2010, Fridriksson et al., 2011). In one study, the S-tDCS (sham) group improved ~1.2 point from baseline to 1 week (Baker, Rorden, & Fridriksson, 2010). In another study, the S-tDCS group improved ~3.9 points from baseline to 1 week (Fridriksson et al., 2011). For power calculations, we assumed the mean change from baseline to immediate (1 week) post-testing for the A-tDCS group under the

null hypothesis of non-futility is equal to $m_s+d=4+1.5=5.5$. When the sample size is 33 per group, a two sample t-test with a 0.10 one-sided significance level will have 85% power to reject the null hypothesis that the A-tDCS treatment is 1.5 points better than S-tDCS (sham) and declare futility when the A-tDCS treatment comes from a distribution with mean change of 4 (assuming the pooled SD is 2.6). As with most clinical studies, a certain amount of drop-outs (including subject withdrawal or lost-to-follow-up) can be expected. In preliminary studies less than 5% of visits were missing. Conservatively assuming the drop-out rate to be no more than 5% over 5 weeks, the required sample size was inflated from 33 to 37 per treatment arm to account for the effect of the drop-outs in the intent-to-treat analysis using an inflation factor (Friedman, et al, 1985).

3.4.4 Multiplicity

Since this is a phase II study, the false positive error rate has been relaxed (Schoenfeld 1980). For a futility design the type I and type II error rates are reversed as compared to a traditional, superiority hypothesis. For the primary analysis, the probability of incorrectly declaring a drug futile is 0.1 (or 10%, type I error is the false negative rate). Given that the active tDCS comes from a distribution with a mean change of the control group (e.g. the treatment is the same as the sham), the probability of incorrectly moving to a Phase III trial is 0.15 (or 15%, type II error is the false positive rate).

For secondary outcomes and safety analyses, no adjustment of Type I error probability will be considered, since they will be treated as exploratory.

3.4.5 Missing Data

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the primary outcome measure, can be problematic. For the primary futility analysis we will impute missing data using multiple imputation (Rubin, 1987) assuming a monotone missing mechanism and missing is at random (MAR). Similar methods will be employed for secondary analyses and secondary outcomes. For safety data (e.g. AEs) no data imputation will be done.

3.4.6 Interim Analysis

No formal interim analyses are planned.

3.4.7 Adjusting for Covariates

The primary analysis will be adjusted for clinical site, aphasia type, and baseline aphasia severity (AQ).

3.5 Secondary Analyses

3.5.1 Secondary Efficacy Outcome measures

In addition to the primary outcome, several secondary analyses will be conducted. We will examine changes in types of naming errors (defined by the PNT) by tDCS treatment group. The Cinderella story will be analyzed by comparing lexical diversity (VOCD) for nouns, verbs and adjectives; number and types of errors; length and patterns of pauses by treatment group. Pre and post comparisons with both non-aphasic and aphasic speakers from the Aphasia Bank database who share a number of demographic features (e.g., type and severity of aphasia, age, etc) will also be made.

At the end of the study, for the interval scale variables, mean change from baseline to

immediate post-testing in secondary outcome measures will be reported by treatment group along with the 95% confidence intervals. Treatment comparisons will be made with a paired t-test. For binary variables, the proportion of subjects immediately post-testing will be reported by treatment group along with the 95% confidence intervals.

3.5.2 Post-Testing Phase

The longer follow-up post-testing phase will provide exploratory information on whether the immediate post-testing improvement after 3 weeks of treatment can be sustained. The mean (95% CI) changes from baseline to immediate (within 1 week) post-testing, 4 weeks post-testing and 6 months post-testing will be reported. Box and whisker plots will be produced to show the distribution of naming accuracy over time by treatment group. To explore the longitudinal data, a general linear mixed model (GLMM) will be constructed by tDCS group for the dependent variable (anomia). The GLMM will incorporate random subject effects to account for repeated measurements being made on subjects; the model will include time, aphasia type, severity, and clinical center as independent variables. A similar modeling approach may be applied to other secondary outcomes.

3.6 Safety Analyses

All adverse experiences will be summarized in terms of frequency, severity and relatedness to the study treatment using the MedDRA code. All subjects who received tDCS will be included in the safety analysis. At the end of the study, the cumulative incidences of adverse events are compared between the two treatment groups using Fisher's exact test at the two-sided alpha level of 0.05.

The repeated measures of the FACES pain rating scale will be compared by treatment group by fitting a repeated measures proportional odds model.

3.7 DSMB Reporting

The study biostatistician will generate closed and open DSMB reports semi-annually or more frequently, as determined by the DSMB. Each DSMB report provides cumulative summary statistics on enrollment; subject status in the study (e.g., number completed study, drop outs, etc); baseline characteristics; safety data, including AEs and SAEs; and data quality information. The statistics for the closed DSMB Reports are provided by treatment group displayed as A or B. The open report contains aggregated statistics only, i.e., not by treatment group.

3.8 Offsite Collaborators

Dr. Brielle Stark at Indiana University (IU) will serve as an offsite collaborator. She was a postdoctoral fellow in the Aphasia Lab, where she began analysis on data acquired from this study. Her lab will assist with neuroimaging analysis, and analysis of behavioral data and a DTA/MTA is in place to allow sharing of participant video recordings and MRI data. A copy of the MTA agreement is uploaded along with this protocol. All individuals in her lab have CITI training at Indiana University. Data shared with Dr. Stark will be stored in a HIPPA Compliant Box Health account available to her via IU.