STATISTICAL ANALYSIS PLAN

C-STAR Project 2
Stimulating Language in Subacute StrokE (SLISSE)
NCT02674490

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1. LIST OF ACRONYMS

- A- tDCS Anodal transcranial direct current stimulation
- AE Adverse Event
- AQ Aphasia Quotient
- ASRS Apraxia of Speech Rating Scale
- BNT Boston Naming Test
- CU Content Units
- DCU Data Coordination Unit
- fMRI functional Magnetic Resonance Imaging
- HANA Hopkins Action Naming Assessment
- mITT Modified Intent-to-Treat
- MRI Magnetic Resonance Imaging
- MEDdra Medical Dictionary for Regulatory Activities
- mRS modified Rankin Scale
- NIHSS National Institute of Health Stroke Score
- PNT Philadelphia Naming Test
- PPTT Pyramids and Palm Trees Test
- S- tDCS Sham transcranial direct current stimulation
- SAE Serious Adverse Event
- SALT Speech and Language Therapy
- SAP Statistical Analysis Plan
- SIS-16 Stroke Impact Scale -16
- SLP Speech Language Pathologist
- WAB-R Western Aphasia Battery- Revised
- WebDCU™ Web-based Clinical Trial Management System

2. STATISTICAL ANALYSIS PLAN AND STATISTICAL REPORTS

This document provides the details of the statistical analyses planned for the trial. Prior to locking the database and breaking the code, this Statistical Analysis Plan (SAP) will be updated. The final SAP will define all "pre-specified, pre-planned analyses" and will trump the protocol.

3. SYNOPSIS OF THE STUDY

A Randomized, Single-Center, Double-Blind, sham-controlled, Efficacy Study of tDCS combined with SALT for stroke-induced aphasia patients.

4. STUDY DESIGN AND OBJECTIVES

Subjects will be randomized 1:1 to A-tDCS or S-tDCS, with the goal of having 50 randomized subjects for whom the PNT was collected at 1 week post-treatment. This study design will allow us to assess whether A-tDCS over targeted region coupled with computer-delivered SALT is associated with greater gains in accuracy in naming pictures, compared to sham combined with the same computer-delivered SALT in post stroke aphasia.

The primary objective of the study is to determine whether A-tDCS coupled with SALT will improve naming performance of participants with post stroke aphasia more effectively than SALT alone (i.e., the sham condition).

Planned enrollment duration: approximately 4 years (1.04 patients /month)
Duration of treatment phase: 3 weeks
Duration of follow-up in post-treatment Phase: 20 week post treatment (i.e. 23 weeks from baseline)

5. DEFINITION OF TARGET POPULATION

5.1 Target Population

Patients with aphasia diagnosis who experienced an acute ischemic, left hemisphere stroke within 90 days.

5.2 Modified Intent-to-Treat Sample

All analyses will be done using the modified intent-to-treat principle (mITT). Under this principle, the evaluable sample will include all randomized participants for whom study treatment was initiated (e.g. attended at least one treatment session), regardless of the treatment actually received. Participants will be analyzed according to the group to which they were randomized. For secondary and exploratory analyses, missing data will not be explicitly imputed.

5.3 Completers Sample

The primary analysis will be repeated using the subset of randomized participants for whom for whom study treatment was initiated (e.g. attended at least one treatment session) and the PNT was collected at 1 week post-treatment. Participants will be analyzed according to the group to which they were randomized.

5.4 Safety Analysis Sample

All randomized participants who receive at least one session of the treatment are included in the safety analyses, regardless of the duration of intervention administered. Patients will be classified according to the treatment group that was actually received.

6. RANDOMIZATION AND BLINDING

The study is to be conducted in a double-blind manner. The subjects, the site investigators, and the clinical staff involved in this study will not know the intervention assignment. Select members of the Data Coordination Unit (DCU) will be partially blinded, i.e., they will know the intervention group assignment as A or B, but not whether the patient receives active tDCS (A-tDCS) or sham (S-tDCS).

The randomization will take place centrally via the Trial Website (WebDCU). Subjects will be randomized 1:1 (A-tDCS: S-tDCS). The objective of subject randomization is to protect the randomness of treatment allocation and to prevent serious imbalances in baseline age, aphasia type, and severity (as measured by the Western Aphasia Battery revised WAB-R). The block urn method (Zhao et al. 2011) and the minimal sufficient balancing method (Zhao et al. 2012) will be used. 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.

A "Real-Time" randomization procedure is implemented via the Trial Website on the WebDCU™ System where the clinical center staff enters the baseline (e.g., age, 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 treatment assignment based on the randomization scheme.

7. BASELINE INTERVENTION GROUP COMPARABILITY

Summary statistics for the following baseline variables will be compared between treatment groups. 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.

Baseline Characteristics, Mean (SD); Median (IQR)	Active-tDCS (N=)	Sham-tDCS (N=)	p-value
Age			
Male sex, frequency (%)			
Race, frequency (%)			
White			
Black			
Other			
Hispanic, frequency (%)			
Years of Education			
Stroke Onset to Enrollment (days)			
Aphasia Type, frequency (%)			
WAB-R AQ			
Current use (at randomization), freq (%)			
SSRIs Antidepressants			
Mixed /Atypical SSRIs			
Non- SSRIs Antidepressants			
Anxiolytics/Antipsychotics			
Anticholinergic Agents			
Dementia medications			
Past medical history, frequency (%)			
Chronic Pain			
Average # headaches/month			
Seizures			
Surgery			
Allergies			
Depression			
Diabetes			
Exercise 20 minutes (times/week)			
Exercise prior to stroke (times/week)			
mRS			
NIHSS			
BNT			
ASRS			
PPTT			
PNT correct			
Naming 80			
PHQ-9			
SIS-16			
Hopkins Action Naming Assessment (HANA)			
Content Units (CU)			
Syllable/CU			
Current Occupation			
…….			
……			

8. PRIMARY ANALYSIS

8.1 Primary Outcome

The primary outcome will be the change in the number of correctly named items on the PNT (absolute change from pre-treatment and immediate post-testing). The PNT is 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 between the average of the two pre-treatment assessments to the average of the two post-treatment sessions.

8.2 Statistical Hypotheses

The Primary Hypothesis 1a: A-tDCS over a targeted region coupled with computer-delivered SALT is associated with greater gains in accuracy in naming pictures, compared to sham coupled with the same computer-delivered SALT in post stroke aphasia. To test this hypothesis, we will compare the change in means of outcome measures in the group who received sham versus the group who received tDCS. The primary outcome variable will be change in accuracy of naming untrained items within one week after treatment ends. The null hypothesis is H_0: $\mu_1 = \mu_2$, where μ_1 is the mean change in accuracy of naming untrained items (PNT correct) between baseline and 1 week post-treatment in the A-tDCS group and μ_2 is the mean change in the sham group. The primary analysis will compare change between groups (A-tDCS versus S-tDCS) using multiple regression and will be adjusted for aphasia type (Anomia, Broca, or other type), baseline aphasia severity (AQ), and age. The primary analysis will be performed using both the Completers and Modified Intent-to-treat Samples. If these two analyses are not consistent, then the trial findings will be interpreted with caution.

Sensitivity analyses will be done for the change in accuracy of trained items using the same approach. Naming errors will also be analyzed and categorized as semantic related, semantic unrelated, real words related phonologically, non-words related phonologically, mixed semantic/phonological, abstruse neologisms, and no response. Additional sensitivity analyses will adjust for education and time from stroke onset to time of treatment initiation in addition to the covariates included in the primary model.

8.3 Sample Size Determination

If sample size in each group is 20, (a total sample size of 40), we will have 89% power to detect a difference in means of 23 (the difference between A-tDCS mean change in accuracy, μ_1, of 33 and a sham mean change in accuracy, μ_2, of 10) assuming that the standard deviation of change for both groups is 22.2 using a two group *t*-test with a two-sided alpha of 0.05. These mean changes for tDCS and sham and standard deviation of change are based on the one published sham-controlled study of tDCS combined with SALT in subacute stroke (You et al, 2011).

8.4 Multiplicity

The primary analysis and sensitivity analyses will be tested at two-sided alpha of 0.05. For secondary outcomes, no adjustment of Type I error probability will be considered, since they will be considered supportive of the primary analysis. Tests for interaction with baseline covariates and treatment will use two-sided alpha of 0.10, since they will be treated as exploratory.

8.5 Missing Data

For the primary analysis, for participants who do not complete the 1 week post-treatment assessments, the post-treatment value will be imputed using a multiple imputation approach assuming a FCS missing mechanism and missing is at random (MAR).

As a sensitivity analysis with the modified ITT sample, the primary outcome analysis will be repeated using all available follow-up data (without explicit imputation) in a mixed effects model of the change from baseline in naming accuracy adjusted for baseline (with week (1, 5, or 20 weeks post-treatment) as class variable and a REPEATED statement). The model will include the baseline covariates used for the primary analysis as fixed effects.

The statistical model will be a repeated measures model (SAS® MIXED procedure with REPEATED subcommand) assuming a compound symmetry (CS) covariance structure.

```
PROC MIXED;
  CLASS SUBJID ARM VISITNUM TYPE;
  MODEL CHANGE= ARM|VISITNUM WABAQ TYPE AGE;
    REPEATED VISITNUM / TYPE= CS SUBJECT=SUBJID R RCORR;
  LSMEANS ARM*VISITNUM/pdiff CL;
 RUN;
```

The least square (adjusted) mean for each treatment group, and the 95% confidence interval for the comparison (active vs. sham) will be presented at 1, 5, 20 weeks post treatment.

9. HYPOTHESIS 1B

Hypothesis 1b: To address the hypothesis that the effect of A-tDCS will be greater in subacute stroke than reported in chronic stroke, the mean (95% CI) changes from baseline to 1 week, 5 weeks, and 20 weeks in PNT+Naming 80 after the end of treatment will be reported for the subacute patients enrolled in this project and the chronic patients from the CATES trial (Fridriksson, PI).

A figure of the adjusted mean of adjusted means (95% CI) at each time point for SLISSE Active, Sham using the repeated measures model described above will be shown alongside the adjusted means from CATES Active, Sham.

10. SECONDARY ANALYSES

Secondary analyses will evaluate the effect of A-tDCS vs sham on change in lexical features of discourse, Content Units (CU) and syllables/CU in describing the Cookie Theft picture, HANA, NIH Stroke Scale, SIS, mRS, and PHQ-9.

For continuous measures, the secondary analyses will be adjusted for aphasia type (Anomia, Broca, or other type), baseline aphasia severity (AQ), and age using a linear mixed effects regression to compare treatment groups. The model will include repeated measures of change from baseline to 1, 5, 20 weeks post and visit will be a classification variable with interaction terms for visit*treatment group (SAS PROC MIXED with a REPEATED subcommand).

```
PROC MIXED;
  CLASS SUBJID ARM VISITNUM TYPE;
  MODEL CHANGE= ARM|VISITNUM WABAQ TYPE AGE;
      REPEATED VISITNUM / TYPE= CS SUBJECT=SUBJID R RCORR;
  LSMEANS ARM*VISITNUM/pdiff CL;
 RUN;
```

11. EXPLORATORY SUBGROUP ANALYSES

Exploratory analyses will also examine if any effects of A-tDCS vary across participants with different characteristics such as SSRI use, age (<55 vs. ≥55), education (<11 years completed vs. ≥12 years), time since stroke onset to initiation of treatment (<1 month vs. ≥1 month), and lesion volume. To address this, a regression of change in naming accuracy, which includes main effects and interaction terms with treatment group for these characteristics, will be used. Given the small sample size and since this is a secondary analysis, a significance level of 0.10 will be used to retain main effects or interaction with treatment in the final reported model. Finally, within the tDCS treatment group, we will compare mean change in naming untrained pictures for the fMRI versus the structural placement (CRF501 Q01) subgroups.

```
PROC MIXED;
  CLASS SUBJID ARM TYPE SUBGROUP;
  MODEL CHANGE=ARM| SUBGROUP WABAQ TYPE AGE;

  LSMEANS ARM*SUBGROUP/pdiff CL  ALPHA=0.1;
 RUN;
```

Hypothesis 2a: To test the hypothesis that within the first 3 months after stroke, improvement in naming untrained pictures is negatively influenced by increased time to initiate treatment; but this effect of time is mitigated by taking SSRIs continuously from stroke onset, we will carry out the secondary analysis as initially described above by comparing model 1 with model 2 as follows:

- Model 1 will be a linear regression of change in naming accuracy from baseline to 1 week post-treatment with the following regressor/predictor variables: treatment group (A-tDCS or sham), WABAQ, age, education, time from stroke onset to initiation of treatment (in days).
- Model 2 will include the regressors from models 1 and an indicator of SSRI use since baseline (yes= if patient had used SSRIs continuously from stroke onset, no=otherwise). We predict that in model 1, time from stroke onset to initiation of treatment (in days) will be negatively associated with the response variable. In model 2, we predict that time from stroke onset will no longer be associated with outcome; after adjusting for SSRI use (and all else in the model), the type III test for the effect of time from stroke onset will not be statistically significant and the magnitude of the parameter estimate will change by more than 10%.

Hypothesis 2b: To address the hypothesis that SSRI use since stroke onset is associated with greater gains with all treatments in the subacute period, independently of depression, we will collapse participants across treatment groups, and compare the primary outcome measures for participants who have continuously taken SSRIs to participants who have not taken SSRIs. If SSRI use enhances plasticity at the subacute stage, it might augment the effect of A-tDCS and naming therapy without tDCS. Participants who have taken SSRIs for only part of the time will not be included in the analysis. The adjusted mean change (95% CI) in naming accuracy on untrained stimuli from baseline to 1 week, 5 weeks, and 20 weeks post-treatment for the SSRI-treated and the SSRI-untreated groups will be estimated using a mixed effects model adjusting for treatment group, baseline naming accuracy, time (with week 1, 5, or 20 as a categorical variable and a random effect for subject), and any baseline subject characteristic found to be statistically significant in the primary or subgroup analyses. We will then evaluate the independent effects of SSRI use, depression (measured at each time point with PHQ-9 score of ≥15), and tDCS vs sham on the primary outcome graphically. Although we may not have the power to detect a significant effect of SSRIs, a few studies with similar small numbers have reported significant effects of SSRIs on stroke recovery measured with less sensitive measures such as the mRS. The goal of this exploratory aim is to determine whether or not we need to control for SSRI use in a subsequent clinical trial of A-tDCS in subacute stroke.

12. SAFETY ANALYSES

All adverse events will be summarized in terms of frequency, severity and relatedness to the study intervention using the MedDRA code. All subjects who received at least one session of A-tDCS or S-tDCS will be included in the safety analysis. The cumulative incidences of adverse events will be compared between the treatment groups using Fisher's exact test at the two-sided alpha level of 0.05.

References

You, D.S., Kim, D.Y., Chun, M.H., Jung, S.E., & Park, S.J. (2011). Cathodal transcranial direct current stimulation of the right Wernicke's area improves comprehension in subacute stroke patients. Brain and Language, 119(1), 1-5. doi: 10.1016/j.bandl.2011.05.002.

Zhao W, Weng Y. Block urn design - a new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation. *Contemp Clin Trials*. 2011 Nov;32(6):953-61. Epub 2011 Aug 22. PMID: 21893215

Zhao W, Hill MD, Palesch Y., Minimal sufficient balance--a new strategy to balance baseline covariates and preserve randomness of treatment allocation. *Stat Methods Med Res*. 2012 Jan 26. [Epub ahead of print], PMID: 22287602