Speech Entrainment for Aphasia Recovery

SpARc

Leonardo Bonilha, M.D., Ph.D. and Julius Fridriksson, Ph.D.

Version 14.0

02MAY2024

Table of Contents

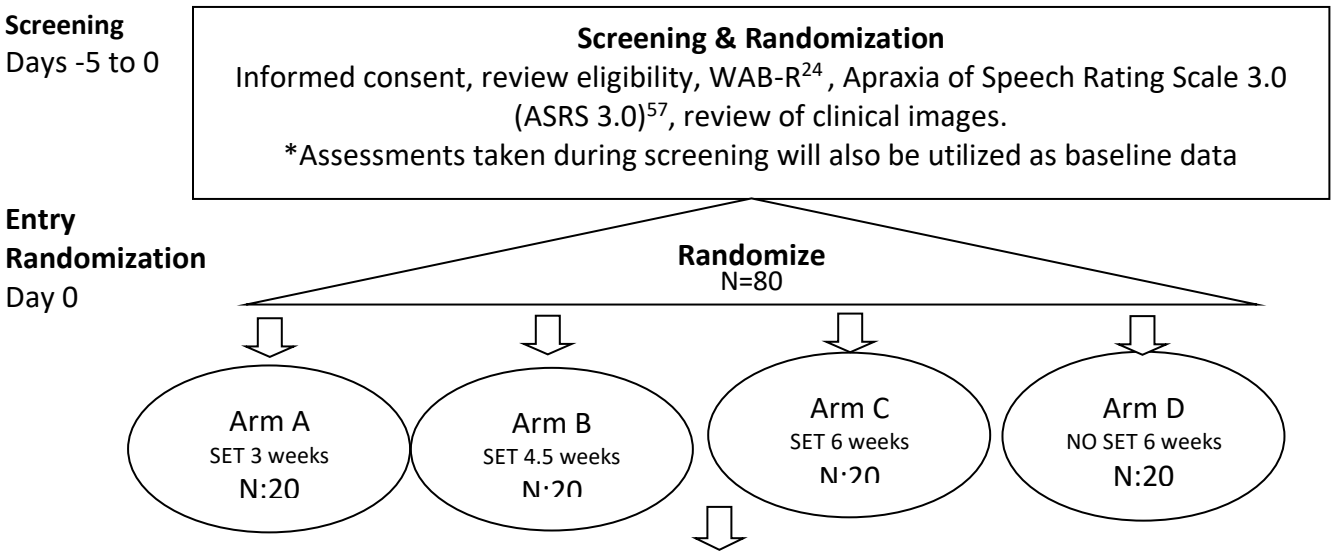
1.0 Protocol Summary

1.1 Synopsis

Title:	Speech Entrainment for Aphasia Recovery
Study Description:	Speech entrainment therapy (SET) targets speech production in persons with non-fluent aphasia and has yielded promising results in phase I trials. SET involves online mimicking of an audiovisual speech model, which allows many non-fluent individuals to practice producing fluent speech. This trial aims to determine the best dose of SET for the treatment of chronic non-fluent aphasia.
Objectives:	Primary Objective: To determine the dose of SET with the highest effect size on speech fluency Verbs Per Minute (VPM).
Endpoints:	Primary Endpoint: VPM at 3 months post conclusion of SET or post no SET period. Secondary Endpoints: Stroke and Aphasia Quality of Life Scale (SAQOL-39g) at 3 months post conclusion of SET or post no SET period.
Study Population:	80 adults (ages 21-81) with chronic (>6 months) aphasia due to left hemispheric stroke.
Phase:	2
Description of Sites/Facilities Enrolling Participants:	There are 3 participating sites: Medical University of South Carolina (MUSC), University of South Carolina (UofSC), and University of Utah (UoU). All sites will be conducting this trial via telehealth.
Description of Study Intervention:	A - SET for 3 weeks (15 days, 1 hour daily, 5 x week) B - SET for 4.5 weeks (22 days, 1 hour daily, 5 x week) C - SET for 6 weeks (30 days, 1 hour daily, 5 x week) D - No-SET for 6 weeks (control condition)
Study Duration:	5 years
Participant Duration:	28-31 weeks dependent on participant group randomization

1.2 Schema

SpARc Flow Diagram



1.3 Schedule of Activities

1.3.1 Screening and Randomization (Visit 0)

Once consented, either in person or eConsent (see section 10.2 for more details about the consent process), participants will be contacted via telephone or email to schedule a screening and randomization telehealth visit. Once scheduled, research staff will email the participant a link to access the secure visit at the set appointment time. All visits will be conducted through a secure, HIPAA-compliant, telehealth platform. The online platform allows researchers to connect to participants in their own homes via video-conferencing.

Research staff will go through the inclusion and exclusion criteria (see section 5.1 and 5.2). Participants will be asked to provide medical records to confirm presence of left hemisphere stroke. This can be done through electronic medical records if available. Presence of right hemisphere, cerebellar, or brainsterm stroke or other structural neurological conditions (such as brain tumors or arteriovenous malformations) with persistent deficits will exclude them from participation in this study. The NIH Stroke Scale (NIHSS) is administered by a trained clinician (speech-language pathologist [SLP] or neurologist) to assess for post-stroke neurological deficits. If the MRI verifies presence of left hemisphere stroke, participants will then be given the Western Aphasia Battery-Revised (WAB-R), a common clinical aphasia assessment to determine the presence of non-fluent aphasia. The Apraxia of Speech Rating Scale 3.0 (ASRS 3.0) will be given to determine presence and severity of dysarthria. The modified Rankin Scale (mRS) will also be administered to determine eligibility (see section 5.1). The Revised Hearing Handicap Inventory-Screening (RHHI-S) will be given to the participant to screen for significant hearing loss. The SLP will consult the RHHI-S score and use clinical judgment to determine if hearing is adequate for the purposes of this trial. The participant must wear any individual corrective hearing devices if applicable.

Videorecordings of assessments will be saved to the researcher's local password protected and encrypted computer. Videos will be immediatley uploaded to a HIPAA-compliant Box account. Once vidoes are confirmed to have been successfully uploaded to the Box account, research staff will immediately delete the video stored on the computer's harddrive. Participants will be asked to have a friend or family member (assistant) present to help with technology.

Once all assessments are complete, and the participant is found to have non-fluent aphasia as well as meets all eligibility criteria (section 5.1 and 5.2), the participant will be randomly assigned to one of four arms (Figure 1):

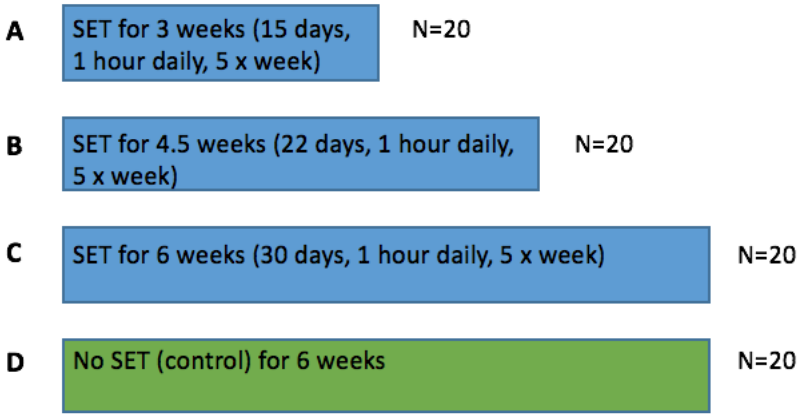


Figure 1. Overall study design. This diagram depicts the 3 different doses of SET (treatment arms) and the control arm. For clarity of visualization, the behavioral assessments are not depicted in this diagram, but are explained in Table 1 (Study Schedule) below. In brief, all participants will receive behavioral assessments one week before the initiation of therapy, then 1 week, 3 months, and 6 months after the conclusion of SET or no SET.

After randomization, a telehealth technology kit will be sent to the participant's home. Each kit will include:

1. A computer pre-loaded with the treatment applications, internet capeabilities for the telehealth platform, and Team Viewer, which will allow the SLP to see the participant's computer to help with initial set-up and troubleshooting.
2. A high-quality headset and microphone to maximize communication with research staff online.
3. A mouse for optional use.
4. A mobile WiFi hotspot if a participant does not have an adequate WiFi connection at home.

Participants will be asked to review and sign the SpARc Telehealth Technology Contract upon receipt of equipment. The Technology Contract will also be created in RedCap so the patient can sign virtually.

1.3.2 Baseline Assessments (Visit 1)

The baseline assessment visit will consist of the tests outlined below. All assessments are adapted to be administered online. A brief training session will take place before the administration of assessments to make sure that the participant and his/her assistant can demonstrate how to use controls in the telehealth platform to point to pictures on a shared screen. The assistant will also be instructed on how to alter the webcam to allow the clinician to view the participant completing different tasks.

Baseline testing (demographic and baseline characteristics can be seen in Table 3 and the remaining assessments in Table 1) will be done in all groups. Per the discretion of the SLP, baseline assessments can be completed over the course of 2-5 days, depending on the participant's ability and stamina. Descriptions of baseline assessments can be found in section 1.4, Study Assessments. Instructions for administering assessments can be found in specific assessment manuals. The order of baseline assessment administration after screening is as follows:

1. Verbs per Minute (VPM) – discourse assessments
2. Modified Philadelphia Naming Test (PNT)[68]
3. Stroke and Aphasia Quality of Life (SAQOL-39g)[54]
4. Modified Charlson Comorbidity Index[60]
5. Communicative Effectiveness Index (CETI)[56]
6. Lexical Orthography Familiarity Test (LOFT)[61]
7. Modified Epworth Sleepiness Scale (ESS)[70]
8. Pyramids and Palm Trees Test (PPTT)[58]
9. Matrix Reasoning - Wechsler Adult Intelligence Scale III (WAIS-III)[59]
10. Vertical Numerical Rating Scale-Face Rating Scale for post-stroke fatigue (NRS-FRS)
11. Modified Philadelphia Repetition Test (PRT)[69]
12. Community Stroke Aphasic Depression Questionnaire (SADQ-10)[62]

We will keep the order of test administration constant but will leave it to the clinical judgment of the SLP to determine appointment duration and number of days required for each individual participant to complete testing. Factors that the clinician will consider include severity of aphasia, overall endurance, and tolerance of testing. From experience with prior aphasia trials, these factors can vary between participants.

Schedule for screening, baseline assessments, intervention, and outcome measures can be seen below in Table 1:

Table 1. Schedule of Activities

*Refer to Table 4 for assessment recording and scoring procedures

Assessment	Screening & Randomization Visit 0 Days -5 to 0	Baseline Assessments Visit 1 Days 1-5 (+/-4 days)	Intervention Period Visits 2-30[a] For 3, 4.5, or 6 weeks (+/- 3 days)	Follow-Up Visit 1 1-week post intervention[b] (+/- 3 days)[c]	Follow-Up Visit 2 3-month post intervention[b] (+/- 1 week)[c]	Follow-Up Visit 3 6-month post intervention[b] (+/- 1 week)[c]
Informed consent	X					
Review of eligibility criteria and randomization	X					
Concomitant Aphasia Treatment			X			X
Assess New Adverse Events			X	X		
Verbs per Minute (VPM)		X		X	X	X
Gathering of individual demographic and baseline characteristics (Table 3)		X				
NIH Stroke Scale (NIHSS)	X					
Western Aphasia Battery-Revised (WAB-R)	X[d, e]			X	X	X
Quality of life assessment - Stroke and Aphasia Quality of Life (SAQOL-39g)		X		X	X	X
Charlson Comorbidity Index		X				
Communicative Effectiveness Index (CETI)		X		X	X	
Lexical Orthography Familiarity Test (LOFT)		X				
Modified Epworth Sleepiness Scale (ESS)						
Apraxia of Speech Rating Scale 3.0 (ASRS 3.0)	X[d]			X	X	
Pyramids and Palm Trees Test (PPTT)		X				
Matrix Reasoning - Wechsler Adult Intelligence Scale, Third Edition (WAIS-III)		X				
Vertical Numerical Rating Scale-Face Rating Scale for post-stroke fatigue (NRS-FRS)		X				
Modified Philadelphia Repetition Test (PRT)		X		X	X	
Modified Philadelphia Naming Test (PNT)		X		X	X	
Stroke Aphasic Depression Questionnaire (SADQ-10)		X				
MRI					(optional)	

Footnote: [a]Number of visits depend on randomized arm. [b]Follow-up assessments can be completed over 1-5 days. [c]Definitions for the follow-up visit target date and window provided in Table 2. [d]Repeat WAB-R/ASRS 3.0 measures prior to intervention if initiation of intervention period occurs >15 days post randomization. [e]Use of WAB-R scores obtained for other purposes, administered within 120-days before randomization, is allowed.

Note: In the event of technological difficulties, readministration of baseline or follow-up testing will be conducted within study timeline constraints to maintain the integrity of data collection.

Table 2. Follow-Up Visit Target and Visit Windows in Days

Randomization Assignment	Follow-Up Visit 1	Follow-Up Visit 2	Follow Up Visit 3
SET (any dose)	7 days after the last completed SET session +/-3 days	90 days after the last completed SET session +/-7 days	180 days after the last completed SET session +/-7 days
No SET[a]	54 days post-randomization +/-7 days	137 days post-randomization +/-11 days	227 days post-randomization +/-11 days

Footnote: [a]The No SET target date for follow-up visits accounts for time to complete baseline assessments (5 days), and the window for the follow-up visits is widened to account for the window for baseline assessment visits (additional +/-4 days).

Table 3. Individual Demographic and Baseline Characteristics
1- Age at the time of the stroke.
2- Cardiovascular risk factors (each comorbidity will be collected and the cumulative score will be calculated using the Charlson Index[60])
3- Pre-morbid functioning (Lexical Orthographic Familiarity Test[61], LOFT, a pre-morbid functional tool validated in subjects with aphasia).
4- Post-stroke depression (assessed using the Stroke Aphasia Depression Questionnaire SADQ-10[62]).
5- Post-stroke fatigue – (assessed using the Epworth Sleepiness Scaled[70] modified for those with aphasia[71] and the Visual Analogue Fatigue Scale[72]).
For participant description in publications and secondary analyses, we will also collect information about prior treatment for aphasia (duration of treatment after stroke, type of treatment) as well as socio-demographic information including age, sex, race/ethnicity, handedness, pre-stroke household income, education level, insurance status, and marital status.

Table 4. Scoring and Recording of Assessments

Assessment	**Record and score**	**Record and save to Box, but not scored**	**Scorer**		**No video recording**
			Local site	**Centralized (UofSC)**	
WAB-R baseline	X		X (for eligibility)	X	
WAB-R follow-up visits #1, 2, 3	X			X	

ASRS 3.0 baseline	X		X (qualitatively interpreted for eligibility)	X[a]	
ASRS 3.0 follow-up visits #1, 2	X			X[a]	
VPM follow-up visits #1, 2, 3	X			X	
Demographic and baseline characteristics (Table 3)			X		X
SAQOL-39g baseline			X		X
SAQOL-39g follow-up visits #1, 2, 3			X		X
CETI			X		X
CETI follow-up visits #1, 2			X		X
PPTT			X		X
WAIS-III (Matrix Reasoning)			X		X
PRT baseline	X			X	
PRT follow-up visits #1, 2		X			
PNT baseline	X			X	
PNT follow-up visits #1, 2		X			

Footnote: [a]ASRS 3.0 scored by an expert, blinded assessor at UoU.

1.3.3 Intervention (Visits 2-30)

Participants randomized into one of the three SET treatment arms (A, B, C) will begin intervention Monday-Friday for one hour a day. The no SET arm will not have interventional visits for 6 weeks. For specific details regarding intervention, please refer to section 6.

1.3.3.1 Assessment of Adverse Events

We will ask the participant to report adverse events (AEs) as they occur and will routinely ask the participant at the end of each week of intervention. We will also call each participant in the no SET group weekly to assess AEs. See section 8.2 for more information regarding the definition and classification of AE and guidelines for reporting events.

1.3.3.2 Missed Intervention Appointments

For missed intervention appointments, the participant has the option to make up sessions on weekends or in the days prior to testing.

1.3.4 Follow Up Testing (Follow Up Visits 1-3)

All participants will receive follow-up testing according to the timeline shown in Table 1 above (1 week, 3 months, and 6 months post intervention or no SET). Outcome measures obtained at each follow-up visit are also listed in Table 1. Assessment descriptions can be found in section 1.4, Study Assessments. Follow-up testing will be completed in 3-5 days, dependent on participant ability.

1.3.5 Concomitant Aphasia Treatment

Since we are not restricting behavioral speech and language therapy outside of the SET protocol, we will document concomitant speech therapy each participant is engaged in. We will collect this information at the follow-up visits listed in Table 1. Concomitant aphasia treatment will be obtained from participant and/or caregiver report and categorized by treatment type and frequency. The research team will record this information using Table 5 below.

Table 5. Concomitant Aphasia Treatment

Therapy type	**# Days of therapy from start of intervention until 3-month follow-up**	**# Days of therapy between 3-month follow-up and 6-month follow-up**
Face-to-face with an SLP		
Online or app based program		
Structured support group		

1.4 Study Assessments

Verbs per Minute (VPM)
VPM will be obtained at baseline and follow-up appointments through scoring of one procedural story telling task and one narrative story telling task. VPM from discourse samples provides us with the participant's ability to produce verbs during discourse, which is a meaningful clinical representation of the participant's overall fluency in discourse. VPM is obtained from the off-line transcription of the discourse assessments and subsequent scoring via the automated coding analysis (Computerized Language Analysis [CLAN]) systems available through AphasiaBank[4].

Western Aphasia Battery-Revised (WAB-R)[24]

The WAB-R will characterize the 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. It allows for the differentiation of these specific language abilities, as well as the classification of aphasia type (see Table 6 below). The WAB-R also yields a composite score, the Aphasia Quotient (AQ), which provides an overall measure of severity, in which lower scores denote more severe aphasia[24] (see Table 7 below). For diagnostic purposes, non-fluent aphasia is defined by WAB-R Auditory Comprehension score >4 and WAB-R Fluency score <6, falling under the categories of global, Broca's, transcortical motor, or transcortical mixed aphasia.

Table 6. Aphasia Classification Criteria[24]

Aphasia Type	Fluency*	Auditory Verbal Comprehension	Repetition	Naming and Word Finding
Global	<5	0-3.9	0.49	<7
Broca's	<5	4-10	0-7.9	<9
Isolation	<5	0-3.9	5-10	<7
Transcortical Motor	<5	4-10	8-10	<9
Wernicke's	>4	0-6.9	0-7.9	<10
Transcortical Sensory	>4	0-6.9	8-10	<10
Conduction	>4	7-10	0-6.9	<10
Anomic	>4	7-10	7-10	<10

*In this study we will use a Fluency score of <6 for inclusion of participants with mild or improving non-fluent aphasia as defined by the description of Fluency score 5 in the WAB-R administration and scoring manual.[24]

Table 7. Aphasia Quotient (AQ) and Severity[24]

AQ	Severity
0 < AQ ≤ 25	Very severe
25 < AQ ≤ 50	Severe
50 < AQ ≤ 75	Moderate
75 < AQ ≤ 93.7	Mild
93.7 < AQ ≤ 100	No aphasia

NIH Stroke Scale (NIHSS)

The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of conscioiusness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. Ratings for each item are scored from 0-3 , with 0 as normal.

Stroke and Aphasia Quality of Life (SAQOL-39g)[54]

The SAQOL-39g 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 also breaks down items into different domains: physical score, communication score, and psychosocial score.

Communicative Effectiveness Index (CETI)[56]
The CETI is a self-rated scale of overall communicative effectiveness containing 16 items. It uses a 10cm visual-analogue scale ranging from "not able at all" to "as able as before." The participant points on the scale to self-rate level of severity for each item.

Revised Hearing Handicap Inventory-Screening (RHHI-S)[78]
The RHHI-S is a short screen for hearing handicap that consists of 10 hearing-related handicaps. Participants must utilize personal hearing devices (if any) during the screen. The participant will select a response of "yes," "sometimes," or "no" for each item. The total score is collected based on participant responses:
Yes= 4
Sometimes= 2
No= 0

Apraxia of Speech Rating Scale 3.0 (ASRS 3.0)[57]
The ASRS 3.0 will be utilized to rate the presence and severity of apraxia of speech (AOS) and to screen for severe dysarthria. It quantifies the frequency and severity of the characteristics associated with AOS. It contains 13 items with distinguishing features of AOS and is scored across three separate tasks:

- Spontaneous Speech Tasks (alternating and sequential motion rates, maximum vowel prolongation, word repetition, sentence repetition)
- Spontaneous Speech Subtest of the WAB-R
- Discourse samples (same samples used at baseline for VPM)

Pyramids and Palm Trees Test (PPTT)[58]
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 participant's difficulty in naming or pointing to a named pictured is due to a difficulty in retrieving semantic information from pictures, retrieving semantic information from words, or, in the case of a naming failure, retrieving the appropriate spoken form of the word.[58]

Matrix Reasoning - Wechsler Adult Intelligence Scale, Third Edition (WAIS-III)[59]
The Matrix Reasoning subtest of the WAIS-III is composed of four types of nonverbal reasoning tasks: pattern completion, classification, analogy, and serial reasoning. The participant looks at a matrix from which a section is missing and either identifies by number or points to one of five response options that complete the matrix. This test will allow for analysis of the cognitive status of the patients.[59]

Neuroimaging
We will obtain a release of medical records from the participants to review their peri-stroke brain imaging. Brain MRIs or head CT scans will be reviewed to confirm that the aphasia was caused by a left hemisphere stroke. As explained in the inclusion and exclusion criteria, we will exclude individuals with previous strokes outside the left hemisphere. An optional brain MRI will be offered to participants at

follow-up visit #2 (3-months post-intervention) or #3 (6-months post-intervention). This MRI scan will include high-resolution structural brain imaging to evaluate the stroke lesion anatomy in more detail.
Philadelphia Naming Test (PNT)[68] The PNT is a picture naming task consisting of 175 high- and low- frequency nouns that vary in length from 1-4 syllables that assess lexical access ability in aphasic participants.
Philadelphia Repetition Test (PRT)[69] The PRT is a test of speech repetition ability. It uses the same items as the PNT, but instead of showing the pictures to the participants, the names of the items are spoken to them (once only), and participants must repeat the names back to the experimenter.
Charlson Comorbidity Index[60] The Charlson Comorbidity Index is an index that collects specific comorbid conditions, including cardiovascular risk factors. Each comorbidity will be collected, and the cumulative score will be calculated.
Lexical Orthographic Familiarity Test (LOFT)[61] The LOFT is a forced-choice recognition task based on lexical familiarity judgments. The participant is shown two words and instructed to choose which word looks more familiar.
Stroke Aphasic Depression Questionnaire (SADQ-10)[62] The SADQ-10 is a questionnaire used to assess depression in individuals with aphasia. The participant and/or caregiver selects the frequency of each depression-related behavior the participant may exhibit.
Modified Epworth Sleepiness Scale (ESS)[70] This is a scale in which the participant rates their level of sleepiness for daily activities from 0 (would never doze) to 3 (high chance of dozing).
Vertical Numerical Rating Scale-Face Rating Scale (NRS-FRS) This is a visual analogue scale that the participant will use to self-rate their level of fatigue ranging from zero (no fatigue) to 10 (worst possible fatigue).
Modified Rankin Scale (mRS) This measures severity of disability for the participant both before and after stroke.

Note: All assessments are modified for online use via telehealth.

2.0 Introduction

2.1 Study Rationale

Aphasia is the neurological impairment defined by the compromised ability to comprehend or produce language[1]. It affects at least 20% of stroke survivors, and many individuals with aphasia persist with chronic language problems (>6 months after the stroke)[2].

Individuals with aphasia who experience difficulties in producing fluent speech are categorized as having non-fluent aphasia[3]. Broca's aphasia, transcortical motor aphasia, and global aphasia are the classical examples of non-fluent aphasia. Unfortunately, non-fluent aphasia is common[4], strongly associated with lower quality of life[3], and notoriously difficult to treat. The majority of subjects with non-fluent aphasia do not achieve satisfactory gains in spontaneous speech with standard of care aphasia therapy[5, 6] and this treatment gap constitutes and important and unmet clinical need, underscoring the importance of new and innovative forms of treatment. In a pilot study (Fridriksson et al., *Brain* 2012)[7], we described a new approach to treat non-fluent aphasia, termed speech entrainment therapy (SET). SET is a form of speech therapy that uses an audio-visual system to guide (entrain) the speech of the person with aphasia. In our original study, we observed that many subjects with non-fluent aphasia overcame the barrier towards fluency and achieved improvements in fluent speech with SET, with normal prosody and without many errors[7]. Since then, we expanded our pilot data and we observed that individuals with non-fluent aphasia treated with SET achieved greater than 20% improvement in verbs per minute (VPM) during spontaneous speech at three months after therapy.

These are very encouraging results because they represent sustained post-treatment gains in producing verbs during discourse, which is a valid ecological measure that is a better predictor of language abilities compared with producing nouns, or object naming[8]. Based on these promising data, we hypothesize that SET may be a meaningful clinical tool for the treatment of non-fluent aphasia. Nonetheless, our preliminary results are based on an uncontrolled study with a limited number of individuals. A controlled study to better understand the full effect sizes of SET could define its best dose and justify future studies of SET versus other forms of therapy. For these reasons, we propose a phase II clinical trial to determine the optimal dose of SET.

2.2 Background

Post-stroke aphasia is a prevalent neurological disability with a negative impact on quality of life. Aphasia is a neurological deficit defined by the impaired ability to process language as a result of brain damage[1]. It is one of the most common forms of neurological disabilities after a stroke[2], typically resulting from injury affecting the language-dominant brain hemisphere[9]. At least 20% of all stroke survivors remain with some degree of long-lasting aphasia[2, 10-12]. Since language is one of the most essential components of human interaction, aphasia has a profound and negative impact on quality of life[13-15]. Post-stroke aphasia often leads to social isolation[13, 16, 17], worse rehabilitation outcomes[18], and depression[15, 17, 19].

2.2.1 Non-fluent aphasia

Individuals with aphasia can exhibit different types of language impairments, and aphasia is classified in accordance with the patterns of linguistic difficulties exhibited by each person[20, 21]. Non-fluent aphasia is defined by significantly reduced speech production, ranging from total mutism to utterances composed of only 3-5 words[22, 23]. Non-fluent aphasia is not only a very common type of aphasia, affecting approximately 40% of all chronic aphasia cases[4], but also one of the most debilitating types. Non-fluent aphasia is frequently associated with profound frustration and depression[3].

Slow speech, effortful speech, frequent pauses, short phrase length, single words, and poor articulation are commonly observed in subjects with non-fluent aphasia[3]. There is not a perfect diagnostic tool for non-fluent aphasia, given the complexity of the symptoms that may lead to fluency problems[3]. Nonetheless, one of the most robust tools for this purpose is the Western Aphasia Battery, revised edition (WAB-R)[24], which, in spite of being relatively general, permits a reproducible agreement across clinicians and researchers. The WAB-R is one of the most commonly used tools in daily practice and basing this current research on the WAB-R will permit a clinical translation in the future[see section 1.4].
This research will focus on the recovery of spontaneous speech and will include all forms of non-fluent aphasia, except for global aphasia. Global aphasia is a very severe form of aphasia, with suboptimal recovery potential and, unfortunately, is rarely associated with improvement in fluency.

2.2.2 Speech Entrainment Therapy (SET)

The basic premise behind most rehabilitation approaches, regardless of the targeted function or modality, is that repeated practice of a specific behavior within the therapy session leads to an increased likelihood that this behavior improves and can be executed outside the rehabilitation setting. This concept is related to the principle of Hebbian learning, which is based on the notion that synaptic strength and functional neuronal connections can be reinforced due to repeated stimulation[36] and new experiences lead to molecular and cellular events that alter synaptic efficacy, leading to reorganization of neuronal circuits[37]. This principle should be considered in the context of aphasia therapy since conventional therapies typically induce numerous speech errors[5, 6]. In fact, treatment-induced errors can often exceed correct responses[31]. Based on the Hebbian learning principles of neuroplasticity, it is possible that repeated errors could, in fact, lead to maladaptive changes and contribute to the persistence of post-therapy errors and non-fluent speech. In contrast with conventional speech therapies, SET enables subjects with aphasia to practice fluent speech with few errors, which is, otherwise, unachievable. This innovative and unique feature of SET differentiates it from other forms of speech therapy. We know of no other method, besides SET, that enables non-fluent aphasic subjects to produce fluent, prosodically accurate, speech for a prolonged period of time.

2.2.3 Overcoming learned nonuse

SET also directly addresses the issue of 'learned nonuse,' which implies that stroke survivors tend to avoid using affected functions because doing so is inefficient, relying instead on the spared functions[38]. In the context of motor impairments, learned non-use is manifested by the preferential use of the spared limb, with little or no use of the paretic limb[39]. Although learned nonuse has not been frequently addressed in the aphasia literature, it is clear that non-fluent subjects tend to withdraw from communication situations. SET provides non-fluent stroke subjects with the opportunity to practice fluent speech and reverse some of the effects of learned nonuse in speech.

2.2.4 Theoretical framework and mechanism of action of SET

There is abundant evidence from the current neuroscience literature to suggest that the adult brain is capable of reorganization after injury[40, 41]. Cortical representation, maps, and networks can be modified by new experiences and learning[42, 43]. Nonetheless, reorganization is less likely to occur in brains with larger injuries or in older age[44-46].

The mechanism of action of SET is the sensorimotor transformation of speech, enabling the reproduction of the speech that is heard and seen. It entails the online transformation of auditory and visual signals into articulation and phonological output. As such, SET overcomes (or compensates for) speech production deficits but requires that auditory comprehension to be at least partly intact.

Overall, SET-mediated improvements are likely related to the involvement of brain areas responsible for sensorimotor transformation of speech. Our preliminary data indicate that subjects who benefit the most from SET are those with preserved sensorimotor speech brain areas located in the temporal-parietal junction[7], which is a hub for sensorimotor transformations for vision, movement, and language[47]. Within the left temporal-parietal region, area Spt (left posterior Sylvian region at the parietal-temporal boundary) is specialized in language sensorimotor integrations[48-51]. It plays a similar role in speech compared with other well-known areas responsible for sensorimotor integration of other modalities, such as the lateral intraparietal cortex (area LIP) for eye movement in primates[52], and the anterior intra-parietal cortex (area AIP) for upper extremity reach and grasp[53]. SET-related improvements likely depend on the functional and structural integrity of area Spt prior to therapy.

Nonetheless, SET-mediated recovery may be related to different brain regions depending on the aphasia type. More specifically, for subjects with intact repetition (transcortical aphasia), SET improvement may be related to recruitment of more anterior regions (frontal associative areas).

It remains undefined for whom, why, and how much SET can be of benefit. It is very likely that, within the category of non-fluent aphasia, individuals with different aphasia types (and, thus, with different levels of repetition and comprehension impairment) may benefit differently. For this reason, this study will focus on evaluating whether SET is indeed associated with consistent results, and whether the improvement achieved with SET is comparable with an effect size reported in the literature for conventional speech therapy. If SET is indeed determined to be associated with therapeutic benefits, a “go” decision will be made for a future definitive clinical trial comparing SET with other forms of therapy. During this future study, it will be paramount to determine the individual determinants of therapy success, not only to better inform clinicians, but also to evaluate the mechanisms associated with differential responses from SET versus other forms of therapy.

2.2.5 Evidence-based speech therapy for non-fluent aphasia

One of the most important challenges in establishing evidence-based aphasia treatment is related to the fact that most of the existing literature is based on “small numbers of participants across a range of characteristics (age, time since stroke, and severity profiles), interventions, and outcomes” as described by the 2012 and 2016 Cochrane Reviews[5, 25]. This study aims to directly overcome this challenge by performing a controlled trial with a large number of subjects targeting a specific yet common form of aphasia (non-fluent aphasia).

Although there is evidence suggesting that behavioral treatments for non-fluent aphasia can lead to improvements in spontaneous speech[5, 6, 26-28], it is relatively uncommon for subjects with non-fluent aphasia to recover to a point where their speech could be considered fluent with the existing therapies, particularly in the chronic phases after the stroke[5, 6].

At the moment, there is no completely satisfactory approach for treating spontaneous speech production in non-fluent aphasia, which constitutes an important and unmet clinical gap

in the neurorehabilitation of stroke. This is a well-recognized area for improvement and past and current clinical trials have attempted to assess new approaches to treat aphasia, including Constrained-Induced Aphasia Therapy (CIAT)[29] (ClinicalTrials.gov Identifier NCT00843427), Melodic Intonation Therapy[30] (NCT00903266), transcranial direct current stimulation (tDCS) (NCT01686373), tDCS coupled with Dextroamphetamine (NCT02514044) and transcranial magnetic stimulation (TMS) (NCT00608582, NCT02241213, NCT01512264).

While these are promising new avenues of treatment, we believe that the therapy being proposed in the current trial, speech entrainment therapy (SET), is unique and, perhaps, superior to other forms of therapy because it enables subjects with aphasia to practice relatively error-free, fluent speech. SET guides the reestablishment of speech fluency, thus overcoming the initial barrier between non-fluent to fluent speech, which is not often observed with other therapies.

Moreover, SET may circumvent speech errors that are commonly associated with conventional speech therapies[31]. To the best of our knowledge, the only other form of therapy that induces relatively error-free speech is Melodic Intonation Therapy (MIT)[32, 33]. However, MIT propitiates practice in verbal output with a prosody that is different from actual speech and, therefore, is less ecologically realistic. For this reason, SET may be a better approach to permit practice in fluent speech. The significance and innovation of SET are further explained in detail below.

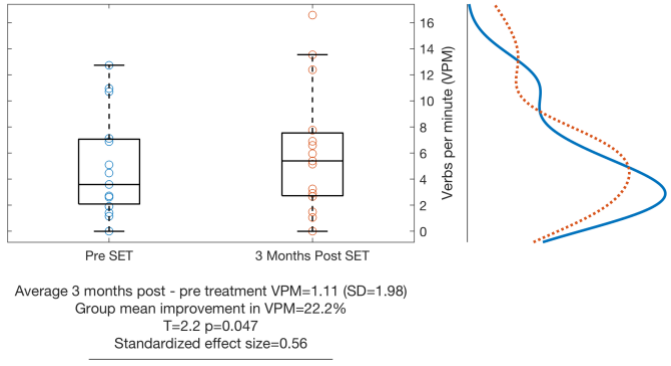


Figure 2. Preliminary data - SET delivered once a day, 5 times a week for three weeks was associated with significant gains in spontaneous speech production, which were sustained at 3 months after the conclusion of SET. The box-plot demonstrates the VPM data before and after SET (with the vertical histograms on the right side to further illustrate the distributions of the data points in the box-plots).

2.2.6 Significance of SET

In a preliminary study[7], we reported SET as a new form of speech therapy to enable individuals with non-fluent aphasia to produce fluent speech. During the SET session, the participant's speech is "pulled along" (guided) by an audiovisual (A/V) model in which the therapist's mouth is seen on a computer screen and the speech is heard via headphones (for an illustrational video, please refer to https://youtu.be/rseSnWq9C_U).

It is important to point out that speech repetition ability and speech entrainment ability dissociate in most participants with non-fluent aphasia. That is, many participants with very poor repetition (as in the case of most non-fluent participants) can still produce fluent speech with speech entrainment. However, it is not known whether SET success depends on the degree of speech repetition impairment, or the degree of auditory comprehension deficits. Our preliminary data provided the "proof of concept" to justify a phase II clinical trial to achieve a detailed assessment of SET effect size and estimate type of linguistic improvements and response variability.

2.2.7 Preliminary study and pilot data for Specific Aim 1

Our supporting data are based on two studies: the first one (preliminary published study, described in more detail below) was published by our group in 2012 in the journal *Brain*[7], and the goal of that study was to determine the feasibility of SET as a clinical approach to treat non-fluent aphasia. That initial study focused on comparing delivery modes of SET and used speech metrics, such as the number of words per minute, and speech fluency ratings from the WAB-R. Subsequently, we determined that, while these measures may be adequate to assess aspects of discourse, they are possibly not the most sensitive measures of the effects of SET, and not the most reliable representations of speech abilities (e.g., a participant may repeat a noun several times but not improve communication). For this reason, we conducted a separate study (pilot data also described in more detail below), which was directly intended to provide preliminary data for this application. This second study used a similar dose of therapy as the current trial (3 weeks) and measured its effects on the same primary endpoint proposed here (VPM).

2.2.8 Preliminary published study

Fridriksson et al. (2012) was a preliminary study by our group, which provided the initial proof of principle for the effectiveness of SET. This study detailed: 1) the creation and implementation of SET using an A/V feedback system; 2) that SET using an A/V model is better than SET using an audio model alone; and 3) the effects of SET on speech production among 13 subjects with chronic non-fluent aphasia after 6 weeks of daily therapy. During SET, the subject used a laptop to view a video of the therapist's face (below the nose), listened to the audio via headphones, and mimicked the speech in real time. The topics were: the weather in the United States, how to make scrambled eggs, or describing the Thanksgiving holiday. Each subject underwent language testing 1 week before and 1 and 6 weeks after therapy. During SET, the subjects' speech was more fluent than their speech outside of therapy. The subjects who underwent SET produced statistically significantly more words during discourse 1 week after treatment ($p<0.05$). They were also nearly better at producing more VPM at 6 weeks after treatment ($p=0.06$), but this effect was limited due to the reduced power from a small sample size.

In Fridriksson et al. (2012), we observed that subjects with aphasia experienced an improvement in overall speech fluency associated with SET (standard deviation=1.7%, t= 2.76, p=0.009). Speech fluency was assessed by tallying the number of different words and recording the percent of correctly produced words per script[7]. In addition, SET was associated with an increase in ratings of information content.

2.2.9 Telehealth as a mode of service delivery

All visits will be performed via telehealth, with the exception of the optional MRI at study completion. The use of telehealth as a successful service delivery mode has been studied in the field of Speech Language Pathology for use with post-stroke aphasia[73-76]. A study by Woolf et al. (2016) compared the effects of Aphasia Remote Therapy (ART), In-Clinic Therapy (I-CT), and attention therapy in a group of individuals with chronic aphasia and found no difference between ART and I-CT. A group study (N=44; 37 had aphasia) conducted by Meltzer et al. (2018) compared I-CT to a hybrid version of ART with one session a week of clinician administered therapy via telerehab, which was heavily supplemented with computerized

homework at least four times a week. This study found hybrid ART to be non-inferior to I-CT. The American Speech-Language Hearing Association (ASHA) also has set up guidelines for telepractice in Speech-Language Pathology[77].

Because SET is already an audiovisual computer program, telehealth will be compatible as a mode of service delivery. Our team has many experienced SLPs specializing in treatment of aphasia and, to our advantage, are already trained in the use of telehealth in aphasia research due to participation in an ongoing study that utilizes telehealth (C-STAR POLAR). This team developed an ART application that has been successfully utilized in POLAR, and this same team has developed an application specific for this trial. Technology support staff will provide on-call technology support for all sites during the trial.

2.2.10 Significance of the knowledge to be gained

Our pilot data suggest that SET can be a groundbreaking, innovative, and clinically feasible approach to treat aphasia. This study will provide a complete and controlled evaluation of SET and provide the important triage before costly head-to-head studies with other forms of speech therapy.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

For the current research, three areas are of paramount interest with regard to the protection of human subjects: 1) Potential adverse effects associated with MRI scanning; 2) Potential adverse effects associated with behavioral testing and treatment; and 3) Maintenance of participant confidentiality. We will address each of these below on a point-by-point basis.

2.3.2 MRI Scanning

All participants have the option to participate in an MRI once they have completed treatment. 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 short-bore magnets (Siemens 3T Trio) 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.

All participants will undergo thorough screening to check for factors counter-indicative for MRI scanning. The optional MRI scanning will not be conducted in participants with contradications. 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 caregiver. Then, we give each participant ample time to get familiar with the scanner before the actual scanning session starts. We find that when taking this extra time to familiarize participants and, when appropriate, family members, with the MRI setup, participants usually feel comfortable with the MRI session.

2.3.3 Participant Testing & Treatment

In our experience, occasional participants will have a negative reaction to neuropsychological testing. For example, this can be caused 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 neuropsychological testing and that participants are allowed

breaks as needed. With regard to the behavioral treatment, the only adverse reaction that we occasionally see is fatigue. This is something that we warn participants about ahead of time.

2.3.4 Participant Confidentiality

All study investigators participating in the current project must ensure that the confidentiality of personal identity and all personal medical information of study participants will be maintained at all times. Additionally, the clinical sites are to follow privacy obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA). Because the DCU uses a web-based system, source documents will remain at site. The study database and any study documents submitted to the DCU 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 (all collected information about a subject will be stored by a unique identification code). All DCU personnel have received GCP and Human Subject Protection training. All participants will be emailed invitations for telehealth appointments and given instructions in advance to join the telehealth session. Any video recordings made during the assessments will be saved to the researcher's local computer and then transferred to a HIPAA-compliant Box account. The central technology support specialist will have access to participant PHI across sites in order to monitor for video quality, manage Box storage, and call into participant sessions for technology assistance.

2.3.5 Known Potential Benefits

There is no real benefit to participation; however, the information gathered as a result of this study may help others with aphasia in the future. It is possible that the participant may benefit from SET treatment, but not guaranteed.

3.0 Objectives and Endpoints

Objectives	Endpoint	Justification
Primary		
To estimate the dose of SET for individuals with non-fluent aphasia that has the highest effect size on VPM.	Verbs per minute (VPM) at 3 months post-treatment/control period.	*See justification below
Secondary		
To estimate the dose of SET for individuals with non-fluent aphasia that has the highest effect size on SAQOL-39g.	SAQOL-39g at 3 months post-treatment/control period	To assess if improvements in fluency from SET are related to gains in quality of life.
Safety and Tolerability		
To assess the tolerability and safety of SET	Number of treatment sessions completed	Adequate tolerability would be completion of at least 80% of the treatment sessions.

	Adverse Events possibly/probably/definitely related to study treatment and Serious Adverse Events	Although this study intervention is low-risk, there is the potential for risk in any clinical trial.
Exploratory		
To estimate the dose of SET for individuals with non-fluent aphasia that has the highest effect size on the WAB-R, CETI, and ASRS 3.0.	Scores at 3 months post-treatment/control period.	To assess if improvements in fluency from SET are related to gains in other speech and/or quality of life measures.
To estimate the effect of SET on VPM, WAB-R, SAQOL-39g at early and late time points.	1-week post and 6 months post	The primary time point of interest is the 3 months post, but the 1 week and 6 month post assessments will be explored to assess whether benefits are sustained over time

*The primary endpoint for this trial is VPM at three months post-conclusion of SET or control. VPM is a measurable representation of spontaneous speech production. This primary endpoint was chosen for the following reasons:
1) Spontaneous speech is an important "real-life" aspect of language. It has a direct effect on conversation and social aspects of language, and directly informs on practical and meaningful elements of communication.
2) The use of verbs during spontaneous speech provides a reliable measure of language abilities and effectiveness of communication[8].
3) It is not surprising that many individuals with aphasia can achieve improved fluency during the SET session. However, for SET to have a clinical impact, it should lead to sustained benefits that remain after the therapy. Benefits that can last at least 3 months after therapy are highly important.
4) Our preliminary data support that improvement in VPM is a feasible and achievable outcome.

4.0 Study Design

4.1 Overall Design

Approach: We propose a prospective, controlled, randomized, assessor-blinded, phase II clinical trial (n=80) entitled *Speech entrainment for Aphasia Recovery (SpARc).* The goals of the trial are to evaluate SET in comparison with no SET (control), and to determine SET's best dose (duration of treatment in weeks). SET and assessments will be delivered via telehealth. We will enroll 80 participants and randomly assign them 1:1:1:1 to one of the 4 groups (A, B, C, D):

A - SET for 3 weeks (15 days, 1 hour daily, 5 x week)
B - SET for 4.5 weeks (22 days, 1 hour daily, 5 x week)
C - SET for 6 weeks (30 days, 1 hour daily, 5 x week)
D - No SET for 6 weeks (control condition)

4.1.1 Timing of Behavioral Assessments

The timing of behavioral assessments after the SET doses, or the control condition (no SET) will exactly mirror each other, so data can be directly compared, and also to permit blinding of the behavioral assessors. The participants will have behavioral assessments at baseline, 1-week post, 3-months post, and 6-months post.

The research staff and the participants will obviously not be blinded to the groups, but the persons doing the scoring of the behavioral outcome measures will be. A scorer will be centrally located at UofSC and will not have contact with the research staff (who will perform the assessments and treatments) and the participants. Another scorer will be located at UoU and will perform scoring of the ASRS 3.0 only. The UoU scorer will not have contact with participants and will also be blinded to treatment arms and assessment time points. All scoring will be performed on videorecorded behavioral assessments stored on Box. By having the same number of follow-up visits, the scorer will not be able to discern the group in which the participant was included. We used this setup successfully in a recently completed randomized controlled trial[35].

4.1.2 Neuroimaging

We will obtain a release of medical records from all participants and we will review the peri-stroke clinical neuroimaging to confirm that the aphasia was caused by a left hemisphere stroke. We will review brain MRI and/or head CT imaging depending on what modality was used during the stroke clinical care. We will use this information to exclude individuals with previous stroke outside the left hemisphere, and we will only include individuals whose aphasia was associated with a stroke diagnosed with neuroimaging.

For neuroimaging fidelity, the PI will oversee review of participant peri-stroke clinical neuroimaging every six months by trained research staff to ensure that MRI/CT images: (1) are uploaded to the site-specific neuroimaging folder in Box, (2) are converted to Nifti files, (3) are anonymized, (4) are T1-weighted (if MRI scans), and (5) show a left hemisphere stroke (without evidence of right hemisphere stroke).

The participants will be offered to take part in an optional research MRI at follow-up visit 2 or 3. The purpose of the research MRI is to study the brain anatomy in more detail, including the necrotic and gliotic cavity related to the previous stroke.

4.2 Scientific Rationale for Study Design

4.2.1 SET vs Control

For SET to be clinically useful, it has to be effective in comparison with a control, no SET condition. The goal of this study is to compare SET with a control condition, in which the individual with aphasia receives baseline and follow-up assessments at the same time-points as group C, however, does not receive therapy for 6 weeks.

Since most individuals with aphasia do not receive continuous speech therapy in the chronic post-stroke stages, it is anticipated most of the control group will not receive treatment

as part of their current standard of care for chronic aphasia. The lack of continuous speech therapy in the chronic stages is, of course, different than in the acute and subacute stages, when continuous speech therapy is often employed. This trial will only assess individuals in the chronic stages. The control condition will provide an important benchmark against variability in speech production across time.

4.3 Justification for Dose

4.3.1 Treatment Groups

In a pilot study, we performed a subsequent and independent assessment of SET to directly mirror the approach proposed in this trial, with a similar endpoint, but uncontrolled and with a single group. Using assessors who were blinded to time of speech assessment (using videorecorded sessions), we examined 15 individuals with chronic non-fluent aphasia who were tested before and after 3 weeks of daily SET sessions. Similar to our published study described above, all participants were able to produce more fluent speech during SET therapy sessions. More importantly, there were considerable gains in spontaneous speech production that were sustained 3 months after SET.

These data, shown in Figure 2, are the main preliminary evidence supporting this study. We observed an increase from an average (± SD) of 5.0 (± 3.9) VPM prior to therapy to 6.1 (± 4.8) VPM at 3 months after the conclusion of SET. The average relative improvement was 22% (average post-pre difference of 1.11 ±SD = 1.98), with a standardized effect size (mean difference/SD of difference) of 0.56. This difference was statistically significant (paired t = 2.17, p = 0.047).

4.3.2 Control Group

The control group will be assessed before and after a six week no-SET condition. During the six weeks there will be weekly contact via phone for assessing AEs and concomitant aphasia therapy. This study will include individuals with chronic aphasia. In the chronic stage, large-scale spontaneous language recovery is not typically observed. External treatment for chronic aphasia is not prohibited in this trial. As discussed, there currently is not a standard of care for chronic aphasia. It is anticipated most participants will receive no treatment, some may participate in aphasia community groups, and a very few may receive individualized therapy. Therefore, the expected change in language functioning during the no-SET condition is expected to be very minimal, if any. Concomitant aphasia therapy will be captured (see Table 5).

The behavioral assessments in the control group will occur at the end of the 6-week no SET period. We will not perform behavioral assessments throughout the no-SET period. For example, in the SET for 3 weeks group, the first post-treatment behavioral assessment will be performed at 1 week after treatment conclusion (4 weeks after initiation of the SET). In the control group, there will not be a behavioral assessment in the middle of the no SET period at 4 weeks (or at other times corresponding to the other groups) because multiple repeated assessments may lead to a training effect. They would also interfere with the blinded assessments. Since we do not anticipate any meaningful improvement in the control group, the treatment assessments at 1 week, 3 months, and 6 months after the no-SET condition will be considered equivalent to the post-SET assessments at the corresponding post SET times for

each SET dose. Using the longest possible control duration of 6 weeks ensures adequate sensitivity to any unanticipated improvement during that period. Having multiple control durations to match the SET durations is, therefore, unnecessary and would lead to a prohibitively and impractical sample sizes.

4.4 End of Study Definition

The randomization target for this study is 80 participants. This trial will be implemented in three aphasia clinical research laboratories across the United States: 1- MUSC, 2- UofSC, and 3- UoU. Each site will enroll approximately 25-30 subjects over 4 years.

5.0 Study Population

We will only include participants with chronic aphasia (>6 months post-stroke) as a result of an ischemic or hemorrhagic left hemisphere stroke. Clinical imaging (CT/MRI) will be used to verify the presence of a left hemisphere stroke and to exclude those with bilateral, brain stem or cerebellar strokes, or other structural neurological conditions (such as brain tumors or arteriovenous malformations). We will not exclude subjects with previous other left hemisphere strokes, but we will exclude subjects with clinical and radiological evidence of right hemisphere or brain stem or cerebellar strokes with persistent deficits. Subjects will not be excluded if they have received previous aphasia rehabilitation, either in the clinical or academic setting.

5.1 Inclusion Criteria

- Aphasia as a result of a left hemisphere ischemic or hemorrhagic stroke (WAB-R Aphasia Quotient <93.8).
- Presence of left hemisphere stroke in clinical imaging (CT/MRI) and NIHSS
- Participants must have spoken English as their primary language.
- 21-81 years old
- Pre-stroke modified Rankin Scale (mRS)= 2 or less
- Post-stroke mRS= 4 or less.
- At least 6 months post-stroke.
- Non-fluent aphasia (WAB-R Comprehension score >4 and WAB-R Fluency score <6).
- Technological compatibility (to be determined by clinical judgment of SLP)

5.2 Exclusion Criteria

- History of chronic neurological or psychiatric diseases (excluding migraines, depression, or post-stroke epilepsy).
- Self-reported history of learning disability.
- Severe dysarthria (determined via SLP clinical judgment from spontaneous speech tasks on the ASRS 3.0).
- Global aphasia.

- History of right-hemisphere strokes or brain stem/cerebellar strokes with persistent deficits (as evidenced by MRI/CT and NIHSS).
- Uncorrectable hearing as determined by the SLP's clinical judgment.
- Uncorrectable vision.

5.3 Screen Failures

Once a participant has consented, they will be screened for eligibility. This includes reviewing the criteria noted in sections 5.1 and 5.2. The team will review imaging (CT/MRI) obtained from the participant's medical records to verify presence of left hemisphere stroke and absence of strokes involving the right hemisphere, cerebellum, and brainstem that have persistent deficits. The NIHSS will be administered by a trained clinician (e.g., SLP, neurologist) to assess for any persistent neurological deficits. The NIHSS will be used for research purposes only. The WAB-R will also be given to determine if eligible based on the Aphasia Quotient and aphasia classification as non-fluent. If the consenting participant fails either of these tests, it will be considered a screen failure and the participant will not be allowed to continue with the remainder of the trial.

All screen failures will be documented in WebDCU, and a hard copy of the Screen Failure form will be stored in a Screen Failure folder, per IRB regulations. Re-screening of participants is not applicable.

5.4 Strategies for Recruitment and Retention

All three participating sites have active aphasia research programs and large recruitment pools for aphasic participants. We will utilize our established participant pool that has agreed to future contact for participation in studies to recruit for this study. These individuals will be contacted by telephone, email, or mail depending on their communication preference. The use of telehealth will likely facilitate strong participant retention rates due to the convenience of in-home therapy.

5.4.1 Advertising

Recruitment will also be performed through local advertisement. We will adopt a strategy that is similar to what was used previously in our large treatment studies where advertisement to rehabilitation centers and clinics has yielded sufficient recruitment. An approved study flyer will be distributed to local clinics, hospitals and rehabilitation centers. Furthermore, we will also advertise to participants who have enrolled in previous aphasia clinical trials at all three sites. If our yield is low, we will update our recruitment plan to use local and state newspaper advertisements as needed. We also plan to advertise studies through statewide directories and site-specific lab websites in addition to university and/or site-specific lab social media accounts, per the IRB of records policies.

5.4.2 Contacting Participants

During the recruitment and initial scheduling period, participants and/or their caregiver/family (as applicable), may be contacted via telephone, email correspondence, or traditional mailing service (whichever is preferred by the participant). Upon establishing

preferred communication preferences, follow-up appointments, changes in schedule, or other pertinent study related information will be relayed in the same manner, as expressed by the participant.

6.0 Study Intervention

6.1 Study Intervention Administration

The administration of SET is relatively simple: Subjects practice imitating in real-time 1-minute scripts that consist of prerecorded videos (A/V speech model). Each video is presented through the SET treatment app made in house that is preloaded on the computer in the teletherapy kit. We will ask the participant or assistant to place the computer (with a high-speed video card) at a comfortable distance in front of the subject, showing a speaker whose face is visible below the nose. Subjects are fitted with headphones to minimize distractions and to better focus on the auditory speech. The A/V speech model involves a relatively slow speech rate and a high-speed video frame rate and the subject is asked to mimic the speech as closely as possible. Subjects usually mimic the speech almost in real-time while seeing and hearing the A/V model. A trained research staff member is present during each session to provide guidance according to pre-established guidelines and to ensure treatment compliance. At the beginning of the first 2-3 treatment sessions, the research staff member models the manner in which the participant should imitate the A/V speech model. The subject instructions are as follows: “Your goal is to speak along with the video and try to match the timing of your speech as closely as possible to the video. If you miss words or fall behind, try to catch up with the video and continue speaking.”

Once subjects understand the approach (as per the judgment of research staff trained by an SLP), the SET session is started. When treatment begins, the participant observes/listens as the videorecorded script is presented in its entirety without mimicking. On successive presentations, the participant mimics the script in real-time. Once a given script (video) has been mimicked three times, a new script is presented and then practiced three times, and so on. Practicing each script three times is based on our experience suggesting that subjects improve considerably from the first to the third practice of a given script. A total of 39 scripts addressing various topics will be constructed. During the treatment session, a new script video is selected at random. In-house computer software is used to accomplish stimulus presentation, start and stop the treatment session, and keep track of treatment data (e.g., the average number of scripts trained per session and how many times a given script was trained during the course of treatment).

6.1.1 No SET condition

During the no SET condition, the participant will not receive any specific form of therapy from the study. The purpose of the no SET condition is to assess whether SET provides a therapeutic benefit over the participants’ current standard of care.

6.1.2 Treatment and assessment setting

Once consent has been obtained and the local research team has established a study schedule for the participant, we will begin baseline testing and subsequent treatment. All baseline cognitive-linguistic testing will be performed via telehealth, and treatment will be

performed through the SET treatment app. We will request that a family member or friend be present during assessment and treatment sessions to assist with technology as needed. Headphones will be used to ensure high quality auditory stimuli. Breaks will be given as needed for those participants in testing or treatment as to not cause fatigue or stress in a new environment.

The optional MRI (at either 3- or 6-months post-intervention) will be performed at the local site's imaging center. Each participant will be provided ample time and orientation from the staff in order to feel comfortable with the scanner and time spent in the scanner.

6.1.3 Dosing and Administration

Treatment dose is dependent on particular group randomization (3 weeks, 4.5 weeks, 6 weeks, no SET).

6.2 Measures to Minimize Bias: Randomization and Blinding Instructions

6.2.1 Randomization

Once the participant is consented and enrolled in the study, his/her information is entered in the online clinical trial management system – Web Data Coordination Unit (WebDCU™). Once the baseline data have been entered in WebDCU, the participant will be randomized to one of 3 SET groups (differing dose) or the control group (Figure 1).

A "Real-Time" randomization procedure will be implemented via the trial website on the WebDCU™ system (located at MUSC). Using the WebDCU™, the local site's study staff will enter baseline and eligibility information for each subject prior to enrollment. If a subject's eligibility status is confirmed, WebDCU™ will make the treatment assignment based on the current status of treatment group distribution at each site, age group (≤70, >70 years), and aphasia severity (mild/moderate: AQ > 50, severe/very severe: AQ ≤ 50), as well as the overall balance of treatment assignments. Once a subject is randomized, the SLP or trained research staff will be made aware of the randomization assignment. The SLP or research staff will videorecord all behavioral assessments, and the recordings will be uploaded to Box at the conclusion of the treatment for centralized scoring.

6.2.2 Blinded assessor

We will employ centralized, blinded outcome assessors, who are comprehensively trained SLP graduate students located at UofSC, to score the videorecorded primary outcome measure (VPM) for all study subjects. Twenty percent of the assessments, including baseline testing and outcome measures, will be scored by a second, independent SLP graduate student assessor to establish inter-rater reliability. In addition, each SLP graduate student assessor will rescore at least 20% of all assessments, for which they were the original primary scorer, to establish intra-rater reliability. Our team has ample experience with aphasia assessments and every measure will be taken to maximize reliability of outcome testing. The primary and secondary coding SLP graduate student assessors will be blinded to the treatment arm. They will also be blinded to when the behavioral measures were obtained (i.e., there will be no time stamps on the assessments, and the assessor will not know if the sample was obtained before SET or no SET, or at which time point after SET or no SET they were obtained).

6.3 Study Intervention Compliance

6.3.1 Subject enrollment, subject assessment, and data entry fidelity

Across all project sites, we will standardize the training of SLPs and trained research staff who administer the cognitive-linguistic and outcome testing, beginning with the development of an assessment manual. We will monitor adherence to assessment administration procedures throughout the 5-year project period. Transcription and scoring of the video and discourse measures will be accomplished in the lab at UofSC, with the exception of transcription and scoring of the ASRS 3.0, which will be completed by an expert scorer at UoU. All discourse assessment sessions will be videorecorded and coded with a unique identifier and uploaded to Box. Scores from videos will be recorded on Case Report Forms (CRFs) maintained in WebDCU™. To maintain reliability, at least 20% of all videorecorded discourse sessions will be re-scored by an SLP.

6.3.2 Participant treatment fidelity

Standardized clinician and research staff training relying upon a detailed manual of treatment procedures will be implemented. Similar to the assessment manual, the purpose of explaining the project and emphasizing the importance of treatment activities is to promote clinician buy-in and subsequent adherence to procedures. The administration of SET is probably no more complex than that of aphasia treatment approaches practiced in everyday clinical practice; it is simply operationalized so that procedures will be standardized across subjects and sites.

6.3.3 Testing and treatment fidelity

It is imperative that we guard against the following threats at each site: variability in clinician and research staff qualifications, drift (gradual change in study procedures over time), contamination (systematic or variable influence of outside factors not controlled for in the study design), and clinician/research staff turnover. A Program/SLP Manager from MUSC will oversee testing and treatment fidelity procedures across all sites.

Ratings of testing/assessment video recordings will be conducted by a Program/SLP Manager or another experienced SLP at MUSC. The rater will observe assessment and treatment video recordings for SLPs across each study site, document fidelity adherence via the SpARc SLP Assessment and Treatment Fidelity Observation Forms, and provide written feedback to clinicians to ensure fidelity of assessment and treatment administration across sites. If necessary, additional training and support will be provided to clinicians by the Program/SLP Manager or another experienced SLP at MUSC.

7.0 Study Intervention Discontinuation and Participant Discontinuation or Withdrawal

7.1 Discontinuation of Study Intervention

The Principal Investigator (PI) at each site has the authority to discontinue a person's participation in the trial at any time if in the participant's best interest; however, the failure to adhere to the study protocol should not be considered a reason for withdrawing a participant from the study. All participants randomized will be included in the analysis, and participants

who withdraw from the study will not be replaced. Participants who wish to discontinue the study intervention or who do not return for follow-up visits should be contacted about participating in follow-up visit(s), so that at a minimum the primary outcome can be collected.

7.2 Participant Discontinuation/Withdrawal from Study: Instructions

- During initial consent, it will be made clear that protocol adherence is of utmost importance to participation in the trial. This is clearly stated in the consent document.
- During the trial, if the participant is not adhering to protocol (e.g., excessive tardiness and cancellations), this will be discussed with the participant and caregiver.
- If the participant still does not comply, the PI will be notified.
- The PI has the final decision to discontinue participation due to safety reasons.

The participant can decide to withdraw at any time. If the participant withdraws from the study voluntarily:

- The PI will be notified.
- Withdrawal status will be appropriately documented, per IRB regulations
- If they chose not to withdraw and still have 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. Refer to section 9.4.4.

7.3 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.

8.0 Study Assessments and Procedures

8.1 Efficacy Assessments

8.1.1 Baseline measures

The WAB-R will be obtained at participant screening to determine if the participant fits criteria for non-fluent aphasia (WAB-R Comprehension score > 4 and WAB-R Fluency score < 6). See Table 6 for aphasia classification chart. If the participant does not classify as having non-fluent aphasia, this is considered a screen failure. The participant will undergo an MRI to determine stroke eligibility criteria, unless MRI images from the stroke are made available to the study team for review. The ASRS 3.0, PPTT, and WAIS-III will be obtained for the purpose of linguistic assessments and participant description in publications. The ASRS 3.0 measures the presence and severity of AOS[57]; the PPTT assesses amodal semantic processing of nouns[58]; and the WAIS-III measures non-verbal abstract problem solving and inductive and spatial reasoning[59]. The SAQOL-39g will be given to assess quality of life for each individual with aphasia. All baseline language assessments will be videorecorded for offline scoring. Recording will include the participant from head to torso, and all recordings will be stored on Box.

Speech repetition and comprehension: We will employ detailed measures of speech repetition and comprehension to refine the identification of subtypes of aphasia and improve the evaluation of the influence of these variables on the effectiveness of SET. As part of the WAB-R, participants will complete the repetition subtest involving single words, phrases, as well as shorter and longer sentences. In addition, all participants will be administered the PRT, involving real words. For detailed assessment of auditory comprehension, we will rely on subtests from the WAB-R.

The mechanisms of action of SET will be determined from the comprehensive behavioral assessment as described in Table 1 above. More specifically, we will define whether fluency improvements with SET are supported by repetition, speech comprehension, or residual fluency, based on the multi-faceted speech and cognitive evaluations.

8.1.2 Primary outcome – VPM

All recorded discourse measures will be stored on Box and scored centrally in the lab at UofSC using automated coding analysis systems available through AphasiaBank. We have already used this setup to assess outcome in our original study of speech entrainment[7]. AphasiaBank includes computerized tools to accomplish discourse transcription and analyses, such as Codes for the Human Analysis of Transcripts (CHAT) and Computerized Language Analysis (CLAN)[64].

Speech samples for VPM scoring will be assessed through procedural storytelling and narrative – with four items in each category. The procedural storytelling items are: 1) how to make a peanut butter and jelly sandwich, 2) how to make scrambled eggs, 3) how to brew coffee, and 4) how to wash dishes. The subject will be recorded while describing each procedure. A two-minute time limit will be imposed for each item. The four topics will be randomized with only one topic being presented each time VPM is being assessed without topic repetition. Randomization of topics will be performed in WebDCU™.

The narrative items will be: 1) Cinderella story, 2) Little Red Riding Hood, 3) The Three Little Pigs, and 4) Goldilocks. The participant will be provided with a picture book without text to guide and serve as a reminder of the story, and the participant will be asked to recount the passages of the story as depicted in the book. Similarly, one narrative will be presented at each VPM assessment, and they will be randomized for each participant in WebDCU™.

By combining procedural storytelling and narratives ranging from different topics, a broad sample of discourse abilities will be obtained. They will be scored using automated coding analysis (CLAN) systems available through AphasiaBank. Words Per Minute (WPM) is included in AphasiaBank and our data will be compared against the data from >440 aphasic subjects already included in AphasiaBank. This feature is especially important for determining variance across participants. The outcome assessor will be blinded to group assignment and to when the sample was acquired (at baseline or after each treatment interval).

8.2 Adverse Events and Serious Adverse Events

* Refer to MUSC IRB Human Research Protection Program (HRPP) Guide, Unanticipated Problems and Adverse Events Policy and Procedures, section 4.7 found at https://research.musc.edu/resources/ori/irb/forms.

8.2.1 Definition of Adverse Event

An AE or adverse experience is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. AEs encompass both physical and psychological harms and occur most frequently in the context of biomedical research, although they can occur in the context of social and behavioral research.

An internal AE is an SE experienced by subjects enrolled by the investigator(s) at MUSC or at a site for which MUSC has oversight.

An external AE is an AE experienced by subjects enrolled by investigators at other institutions engaged in a multi-site clinical trial.

8.2.2 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires participant hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Any other AE that, based upon appropriate medical judgment, that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in participant hospitalization, or the development of drug dependency or drug abuse).

8.2.3 Adverse Event and Serious Adverse Event Reporting

AEs will be documented in the participant's chart. An AE will only be reported if it is related to the intervention. The relation to intervention will be determined by the site PI.

SAEs will be documented in the participant's chart AND reported.

8.2.4 Time Period and Frequency for Event Assessment and Follow Up

AEs will be followed up until stabilized or resolution from study entry through end of study.

9.0 Statistical Considerations

9.1 Statistical Hypotheses

- Primary Endpoint:

  VPM at 3 months post treatment

We hypothesize that, compared to participants who receive control, participants who receive SET for 3, 4.5, or 6 weeks for aphasia will have improved VPM at 3 months and that there is an optimal duration of SET therapy. However, this study was not designed to formally test

SET versus control. This study represents the first step in a series of studies which will ultimately test this hypothesis; however, for this study no formal hypothesis tests are planned. The primary analyses will be descriptive statistics of VPM at 3 months and will estimate the effect size of each SET duration and the pooled SET durations versus control adjusting for baseline.

9.2 Sample Size Determination

9.2.1 Sample Size Considerations for Comparison with Control group

This study is not powered to detect statistically significant differences between the chosen SET dose and the control group. The sample size was determined by administrative reasons. This will be the focus of a later and dedicated comparison study once the best dose has been defined.

9.2.2 Sample Size Considerations for Effect Size of SET versus Control group

For each treatment group versus control, we will estimate the standardized mean difference (effect size). The criterion needed to accept any duration is that the effect size is at least 0.36 (a "small" effect size). The rationale for this criterion is that if the pooled standard deviation estimate is large, because of the small sample size, then the effect size may be smaller than expected. We consider a 20% improvement from control to be the the minimum clinically important difference (MCID). This corresponds to an increase of 1 VPM based on our pilot data (20% of 5 VPM). Given the MCID and the common SD of change in the VPM estimate from pilot data (SD=2), the expected effect size is 0.5. However, with n=20 per group, the observed SD may be as large as 2.74 based on the one-sided upper 95% confidence interval for the common SD; thus, the observed effect size may be only 0.36.

9.3 Populations for Analyses

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

9.4 Statistical Analyses

9.4.1 General Approach

In general, descriptive statistics will be presented by treatment group. 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).

9.4.2 Analysis of the Primary Endpoint

The primary outcome is VPM, which is a continuous value greater than 0. It is collected at baseline, 1 week, 3, and 6 months post treatment period. The primary analysis will calculate the change from baseline. The statistical model will be a repeated measures model (SAS® MIXED procedure with REPEATED subcommand). The model will include the following fixed effects: categorical visit (1 week, 3, and 6 months post treatment period) by treatment group (class variable) interaction, site, baseline aphasia severity score, baseline VPM and age. The estimated difference (95% confidence intervals) in change between each SET duration group and control

group will be reported as the primary analysis. The standardized mean difference for each SET duration versus control will also be reported and will be used to select the best dose of SET. Since this study is not powered for direct comparison with control, no p-values will be reported. Estimates of the change at 1-week and 6 months obtained from this model are exploratory analyses. Additionally, as an exploratory analysis, the combined SET duration versus control comparison will be tested at a two-sided alpha of 0.05.

9.4.3 Missing Data

The primary analysis will be ITT. All participants randomized will be included in the primary analysis regardless of whether or not they dropped out or discontinued treatment. For the primary analysis, a repeated measures linear mixed model will be fit; this is considered an implicit imputation approach if at least 1 post-baseline assessment is available. However, if baseline is the only assessment available (or if baseline is missing but follow-up available), then a nearest neighbor approach will be used to impute the missing values.

9.4.4 Pre-specified rule to select best SET duration

1- Highest standardized mean difference (effect size) in VPM from baseline to three months post treatment;
2- Adequate tolerability: group average participation in at least 80% of the treatment sessions;
We will select the duration associated with the highest group average VPM at 3 months post treatment, but also had adequate tolerability.

9.4.5 Analysis of the Secondary Endpoint(s)

- Secondary Endpoints:
    - Quality of life assessment - SAQOL-39g
    - Individual components of the primary outcome:
        - VPM on Narrative Story Telling Task
        - VPM on Procedural Story Telling Task

The SAQOL-39g will be analyzed similarly to the primary endpoint. The same approach will be used to define the analysis sample and handling of missing data. The mean change from baseline of each SET group will be compared to control with 95% confidence intervals. Since this study is not powered for direct comparison with control, no p-values will be reported.

9.4.6 Safety Analyses

Monitoring Plan for Worsening in the Primary Outcome: If SET leads to substantially worse outcome than the no SET arm, early stopping may be considered. The unblinded statistician will fit the primary analysis model semi-annually in order to compare VPM between the combined SET durations versus No SET (one-sided α=0.025). As part of this analysis, outliers will be explored to ensure that the results are not driven by a specific individual. Should the null hypothesis be rejected, an investigation of dose response among the SET arms based on qualitative evaluation (i.e. not statistical) when ordered in terms of dose level will occur. Should a dose response relationship be detected, the unblinded statistician will bring this to the attention of the DSMB and investigators.

All AEs and SAEs are summarized by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) adverse reaction dictionary in terms of frequency of the event, number of subjects having the event. For the Closed DSMB report, severity, and relatedness to the treatment will also be shown by treatment group.

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.

9.4.7 Baseline Descriptive Statistics

Summary statistics of baseline variables (e.g., demographics, time from stroke onset, aphasia type, WAB-R AQ, all baseline assessments) 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).

9.4.8 Sub-Group Analyses

Gender, Race, Ethnicity: All eligible subjects of both sexes and all races and ethnic groups will be approached to participate in the trial. Recruitment and retention of women and minorities will be monitored throughout the trial. Although we do not anticipate differential treatment effects based on sex, race, or ethnicity, our analyses will explore clinically important differences in these subgroups. Randomization should ensure that the allocation to treatment groups is unbiased and balanced between males and females and different racial and ethnic groups. At the end of the trial, the primary analysis will be repeated within sex subgroups and within race/ethnicity groups. If differences in the magnitude of the treatment effect are observed within a sex, race, or ethnicity subgroup, they will be reported to the scientific community.

9.4.9 Tabulation of Individual Participant Data

Individual participant data will not be listed by measure and time point in the final analysis; however, individual participant listings may be included in Data and Safety Monitoring Board (DSMB) reports for purposes of monitoring trial quality.

9.4.10 Exploratory Analyses

Exploratory Endpoints:

Communicative Effectiveness Index (CETI)
Apraxia of Speech Rating Scale (ASRS 3.0)
WAB-R

For the exploratory endpoints, the mean change from baseline to 1 week and 3 months post of each SET group will be compared to control with 95% confidence intervals.

9.4.11 Scoring of speech samples and evaluation of potential confounders

As described above, all baseline and treatment videorecorded discourse samples will be scored centrally at the Aphasia Lab at UofSC using AphasiaBank, with the exception of transcription and scoring of the ASRS 3.0, which will be completed by an expert scorer at UoU. Special care will be taken to evaluate the influence of potential confounders, such as AOS (rated

on the ASRS), speech repetition scores (WAB-R, PRT), single word (WAB-R), and sentence level comprehension[65]. These will be input into the multiple linear regression analyses used to define determinants of the primary outcome as a sensitivity analysis. Since SET has not been systematically studied as a potential clinical treatment, the goal of this project is to determine if SET is associated with a robust effect size regardless of the underlying source of impairment, but it is very likely that cognitive and linguistic factors that vary across persons with non-fluent aphasia may influence SET outcome to different degrees. We will assess these variations and the overall benefit of SET by systematically assessing the effect size of SET and examining individual characteristics that relate to treatment response.

10.0 Regulatory, Ethical, and Study Operational Considerations

10.1 Informed Consent Process

The consent documentation contains all required regulatory elements and has been approved by the central IRB. The consent also contains HIPAA authorization to use and disclose (release) medical information.

10.2 Consent Procedures and Documentation

Informed consent can be obtained in written fashion by one of the members of the study team. Participants will be provided with ample time to review the consent document prior to discussion with a member of the study team. The nature of the study will be explained by a member of the study team in lay terms. If the potential participant agrees to participate in the study, they will sign and date the informed consent and HIPAA forms (or combined consent/HIPAA if applicable). They will also be informed that they may choose to withdraw from the study at any time. Participants will be informed that their decision regarding participation will not affect their clinical care in any way. A copy of the signed informed consent and HIPAA will be provided to participants.

Alternatively, electronic consent (eConsent) will be obtained through the REDCap system. A member of the research team will reach out to the participant by phone to provide details of the study. If the participant agrees to participate, a link to the REDCap eConsent will be provided to the participant via a hyperlink (text or email), and a member of the study team will review the consent document over the phone or via videoconferencing with the participant. The participant will electronically sign the eConsent and submit the REDCap survey. The study team member will then electronically sign the eConsent and print a PDF of the document. The signed PDF willl be emailed or mailed to participants for their records. eConsent will be implemented at sites that support this method of consent.

10.3 Study Discontinuation and Closure

If the study is prematurely terminated or temporarily suspended, the PI will promptly inform study participants, the IRB, and sponsor and provide the reason(s) for the termination or temporary suspension. When a study is prematurely terminated, refer to Section 7, Study Intervention Discontinuation and Participant Discontinuation/Withdrawal, for handling of enrolled study participants.

10.4 Confidentiality and Privacy

Each participant will be given an identification number through the WebDCU™ and all baseline and outcome measure data will be linked to this number without any identifying information of the participant. Each participant will have a binder that will contain demographic and baseline characteristics (refer to Table 3). The person obtaining this information will have gone through CITI research ethics training and been approved by the IRB. All binders with identifying information will be stored in a locked location at the site. Assessments will be performed via telehealth and videos of participants that have been recorded will be stored on Box, MUSC's approved cloud storage device. Only those who are IRB approved will have access to these videos. A central technology support specialist will have access to participant PHI across sites in order to monitor audio/visual quality of videos and assist with technology with participants in real-time

10.5 Future Use of Stored Data

Data stored on Box and WebDCU™ will be used for data analyses while the study is actively enrolling and after enrollment has ended. All data stored on WebDCU™ will be de-identified with each participant having their own unique identifier. Audio-video recordings of participants will be stored on Box, and only those who are IRB approved will have access to these recordings.

10.6 Key Roles and Study Governance

The clinical trial will be centrally coordinated by the Lead Investigator, Leonardo Bonilha. Participating sites include UofSC and UoU. The Data Coordination Unit (DCU) at MUSC is a nationally renowned center that provides assistance with the design of clinical trials, analysis of clinical trial data, as well as establishing, implementing, and maintaining data and project management systems for multicenter clinical trials, administrative, and statistical support. The DCU will provide the data management backbone for this trial, including online data collection forms, data collection guidelines, continuous data surveillance, and AE reporting.

10.7 Safety Oversight

A DSMB will provide the safety oversight for this trial. The DSMB meets annually to review safety data and trial progress.

10.8 Clinical Monitoring

10.8.1 Site Initiation Procedure

A site initiation visit by the PI and Project Manager will occur to ensure that the following steps are performed in accordance with a unified protocol: 1) participant enrollment, 2) use of the WebDCU™ system, 3) behavioral assessments, 4) intake of individual characteristics, 5) neuroimaging acquisition, and 6) speech therapy. We also implement yearly online recertification for the SLPs and trained research staff to review the SET procedures with the site SLPs and study coordinators and ensure continued proficiency of the study protocol.

10.8.2 Treatment manual, on-site training and online recertifications

The SLP Manager and the Project Manager will create a manual for standard operating procedures (SOPs), and for the administration of the behavioral assessments and of SET. This manual will be shared at the initiation of the study and subsequently throughout the study. The manual and the SOPs will be reviewed through site recertifications.

The SLP Manager and the Project Manager will perform site recertifications every 6 months. This will be done separately and more frequently than site visits, and will be performed via teleconference through the MUSC's Telehealth Center. The MUSC's Telehealth Center is an initiative that supports telehealth activities in diverse applications including health care and research. The Center coordinates training in the use of telehealth technologies for each site, assists with ongoing quality maintenance, and facilitates the administrative management of telehealth activities. We will use a HIPAA-compliant virtual platform for site communication and recertifications. During the recertification process, the SLP Manager and the Project Manager will teleconference with the site study coordinator, and the site SLP and review the manual and SOPs. They will run through case scenarios to ensure understanding of the procedures and answer questions. They will also review data entry and storage compliance, whilst data management is performed independently by the MUSC DCU.

10.9 Data Collection and Management Responsibilities

The research team will be trained by the SLP Manager on methods for data collection. Source documents for assessments will be stored in local site's lab. Training will be provided to research team for use of WebDCU™ online data storage. The SLP Manager will do routine, periodic review of source documents and data stored on WebDCU™ to ensure proper documentation and storage of all data.

10.9.1 Sharing of Results with Subjects

If there are any significant new findings during the course of the study, the participants will be notified. Participant may also request copies of assessment documentation or MRI for their own use or to provide to their primary care physicians. Informal verbal request is all that will be required to obtain documents. All assessments are de-identified as they are recorded by participant number. Each participant will receive a follow-up appointment after study completion to discuss results of study participation. This is not mandatory, but with experience from previous aphasia trials, participants typically request this meeting.

10.9.2 Protocol Deviations

A Protocol Deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initial implementation and occurs when a member of the study departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval.

What are not considered to be protocol deviations are changes or departures from the study design or procedures that are due to a study participant's non-adherence. This should not be submitted to the IRB. This should be documented in a Note to File for the participant records.

In the event of a Protocol Deviation, the research team member should contact the SLP Manager at MUSC and provide details of the deviation. The SLP Manager will then initiate the protocol deviation procedure.

11.0 References

1. Damasio AR. Aphasia. The New England journal of medicine 1992;326:531-539
2. Engelter ST, Gostynski M, Papa S, Frei M, Born C, Ajdacic-Gross V, Gutzwiller F, Lyrer PA. Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. Stroke 2006;37:1379-1384
3. Poeck K. Fluency. In: Code C, ed. The characteristics of aphasia. Philadelphia: Taylor & Francis, 1989: 23-32.
4. MacWhinney BF, D.;Forbes,M.;Holland,A. AphasiaBank: Methods for Studying Discourse. . Aphasiology 2011;25:1286-1307
5. Brady MC, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2012;5:CD000425
6. Kelly H, Brady MC, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2010:CD000425
7. Fridriksson J, Hubbard HI, Hudspeth SG, Holland AL, Bonilha L, Fromm D, Rorden C. Speech entrainment enables participants with Broca's aphasia to produce fluent speech. Brain 2012;135:3815-3829.3525061
8. Rofes A, Capasso R, Miceli G. Verb production tasks in the measurement of communicative abilities in aphasia. Journal of clinical and experimental neuropsychology 2015;37:483-502
9. Croquelois A, Bogousslavsky J. Stroke aphasia: 1,500 consecutive cases. Cerebrovascular diseases 2011;31:392-399
10. Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Aphasia in acute stroke: incidence, determinants, and recovery. Annals of neurology 1995;38:659-666
11. Wade DT, Hewer RL, David RM, Enderby PM. Aphasia after stroke: natural history and associated deficits. J Neurol Neurosurg Psychiatry 1986;49:11-16.1028640
12. Siirtola M, Narva EV, Siirtola T. On the occurrence and prognosis of aphasia in participants with cerebral infarction. Scand J Soc Med Suppl 1977;14:128-133
13. Hilari K, Needle JJ, Harrison KL. What are the important factors in health-related quality of life for people with aphasia? A systematic review. Archives of physical medicine and rehabilitation 2012;93:S86-95
14. Hilari K, Byng S. Health-related quality of life in people with severe aphasia. Int J Lang Commun Disord 2009;44:193-205
15. Kauhanen ML, Korpelainen JT, Hiltunen P, Maatta R, Mononen H, Brusin E, Sotaniemi KA, Myllyla VV. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovascular diseases 2000;10:455-461
16. Black-Schaffer RM, Osberg JS. Return to work after stroke: development of a predictive model. Archives of physical medicine and rehabilitation 1990;71:285-290

17. Code C, Hemsley G, Herrmann M. The emotional impact of aphasia. Seminars in speech and language 1999;20:19-31
18. Hilari K. The impact of stroke: are people with aphasia different to those without? Disabil Rehabil 2011;33:211-218
19. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, Sharpe M. Depression after stroke and lesion location: a systematic review. Lancet 2000;356:122-126
20. de Freitas GR. Aphasia and other language disorders. Front Neurol Neurosci 2012;30:41-45
21. Holland AL, Fromm DS, DeRuyter F, Stein M. Treatment efficacy: aphasia. Journal of speech and hearing research 1996;39:S27-36
22. Geschwind N. The Organization of Language and the Brain: Language disorders after brain damage help in elucidating the neural basis of verbal behavior. Science 1970;170:940-944
23. Gleason JB, Goodglass H, Green E, Ackerman N, Hyde MR. The retrieval of syntax in Broca's aphasia. Brain Lang 1975;2:451-471
24. Kertesz A. The Western Aphasia Battery - Revised. New York: Grune & Stratton, 2007.
25. Brady MC, Kelly H, Godwin J, Enderby P, Campbell P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev 2016:CD000425
26. Fridriksson J. Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. J Neurosci 2010;30:11558-11564.2938788
27. Fridriksson J, Baker JM, Whiteside J, Eoute D, Jr., Moser D, Vesselinov R, Rorden C. Treating visual speech perception to improve speech production in nonfluent aphasia. Stroke 2009;40:853-858.2679690
28. Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of participants with chronic Broca's aphasia undergoing intense intonation-based speech therapy. Ann N Y Acad Sci 2009;1169:385-394.2777670
29. Szaflarski JP, Ball AL, Vannest J, Dietz AR, Allendorfer JB, Martin AN, Hart K, Lindsell CJ. Constraint-Induced Aphasia Therapy for Treatment of Chronic Post-Stroke Aphasia: A Randomized, Blinded, Controlled Pilot Trial. Medical science monitor : international medical journal of experimental and clinical research 2015;21:2861-2869.PMC4588672
30. Norton A, Zipse L, Marchina S, Schlaug G. Melodic intonation therapy: shared insights on how it is done and why it might help. Ann N Y Acad Sci 2009;1169:431-436.PMC2780359
31. Boyle M. Stability of Word-Retrieval Errors With the AphasiaBank Stimuli. Am J Speech Lang Pathol 2015;24:S953-960
32. Albert ML, Sparks RW, Helm NA. Melodic intonation therapy for aphasia. Archives of neurology 1973;29:130-131
33. Sparks RW, Holland AL. Method: melodic intonation therapy for aphasia. J Speech Hear Disord 1976;41:287-297
34. Cramer SC. Stimulating Dialogue Through Treatment of Poststroke Aphasia With Transcranial Direct Current Stimulation. JAMA Neurol 2018
35. 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
36. Hebb DO. The organization of behavior; a neuropsychological theory. New York,: Wiley, 1949.

37. Lowel S, Singer W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. Science 1992;255:209-212
38. Taub E, Uswatte G, Mark VW, Morris DM. The learned nonuse phenomenon: implications for rehabilitation. Eura Medicophys 2006;42:241-256
39. Mark VW, Taub E. Constraint-induced movement therapy for chronic stroke hemiparesis and other disabilities. Restor Neurol Neurosci 2004;22:317-336
40. Dimyan MA, Cohen LG. Neuroplasticity in the context of motor rehabilitation after stroke. Nature reviews Neurology 2011;7:76-85
41. Starkey ML, Schwab ME. How Plastic Is the Brain after a Stroke? Neuroscientist 2014;20:359-371
42. Wittenberg GF. Experience, cortical remapping, and recovery in brain disease. Neurobiology of disease 2010;37:252-258.2818208
43. Gauthier LV, Taub E, Perkins C, Ortmann M, Mark VW, Uswatte G. Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke. Stroke 2008;39:1520-1525.2574634
44. Lindenberger U. Human cognitive aging: corriger la fortune? Science 2014;346:572-578
45. Popa-Wagner A, Badan I, Vintilescu R, Walker L, Kessler C. Premature cellular proliferation following cortical infarct in aged rats. Romanian journal of morphology and embryology = Revue roumaine de morphologie et embryologie 2006;47:215-228
46. Popa-Wagner A, Carmichael ST, Kokaia Z, Kessler C, Walker LC. The response of the aged brain to stroke: too much, too soon? Current neurovascular research 2007;4:216-227
47. Blanke O. Multisensory brain mechanisms of bodily self-consciousness. Nature reviews Neuroscience 2012;13:556-571
48. Hickok G, Buchsbaum B, Humphries C, Muftuler T. Auditory-motor interaction revealed by fMRI: speech, music, and working memory in area Spt. J Cogn Neurosci 2003;15:673-682
49. Hickok G, Okada K, Serences JT. Area Spt in the human planum temporale supports sensory-motor integration for speech processing. J Neurophysiol 2009;101:2725-2732
50. Isenberg AL, Vaden KI, Jr., Saberi K, Muftuler LT, Hickok G. Functionally distinct regions for spatial processing and sensory motor integration in the planum temporale. Hum Brain Mapp 2012;33:2453-2463
51. Pa J, Hickok G. A parietal-temporal sensory-motor integration area for the human vocal tract: evidence from an fMRI study of skilled musicians. Neuropsychologia 2008;46:362-368.PMC2278046
52. Ipata AE, Gee AL, Goldberg ME, Bisley JW. Activity in the lateral intraparietal area predicts the goal and latency of saccades in a free-viewing visual search task. J Neurosci 2006;26:3656-3661.PMC2367056
53. Grefkes C, Ritzl A, Zilles K, Fink GR. Human medial intraparietal cortex subserves visuomotor coordinate transformation. Neuroimage 2004;23:1494-1506
54. 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
55. Holland AL, Frattali C, Fromm D. CADL-2 communication activities of daily living : examiner's manual, 2nd ed. Austin, Tex.: pro-ed, 1999.

56. 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
57. 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.PMC4254321
58. Howard D, Patterson K. The Pyramids and Palm Trees Test: A test of semantic access from words and pictures. . London: Harcourt Assessment, 1992.
59. Kaufman AS, Lichtenberger EO. Assessing adolescent and adult intelligence, 3rd ed. Hoboken, N.J.: Wiley, 2006.
60. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases 1987;40:373-383
61. 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.PMC2910429
62. Laures-Gore JS, Farina M, Moore E, Russell S. Stress and depression scales in aphasia: relation between the aphasia depression rating scale, stroke aphasia depression questionnaire-10, and the perceived stress scale. Topics in stroke rehabilitation 2016:1-5
63. Choi-Kwon S, Han SW, Kwon SU, Kim JS. Poststroke fatigue: characteristics and related factors. Cerebrovascular diseases 2005;19:84-90
64. Forbes MM, Fromm D, Macwhinney B. AphasiaBank: a resource for clinicians. Seminars in speech and language 2012;33:217-222.PMC4073291
65. Magnusdottir S, Fillmore P, den Ouden DB, Hjaltason H, Rorden C, Kjartansson O, Bonilha L, Fridriksson J. Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: a lesion-symptom mapping study. Hum Brain Mapp 2013;34:2715-2723
66. Proschan MA. Two-stage sample size re-estimation based on a nuisance parameter: a review. J Biopharm Stat 2005;15:559-574
67. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med 1991;10:585-598
68. Roach A, Schwartz MF, Martin N, Grewal RS, Brecher A. The Philadelphia naming test: Scoring and rationale. Clinical Aphasiology. 1996;24:121-34.
69. Dell GS, Schwartz MF, Martin N, Saffran EM, Gagnon DA. Lexical access in aphasic and nonaphasic speakers. Psychol Rev. 1997;104(4):801-38. PubMed PMID: 9337631.
70. Johns MW. A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 1991;14(6):540-545
71. Tseng BY, Gajewski BJ, Kluding PM. Reliability, responsiveness, and validity of the Visual Analog Fatigue Scale to measure exertion fatigue in people with chronic stroke: A preliminary study. Stroke Research and Treatment 2010;1-7.
72. Riley EA, Owora A, McCleary J, Anderson A. Sleepiness, Exertion Fatigue, Arousal, and Vigilant Attention in Persons with Chronic Aphasia. American Journal of Speech-Language Pathology 2019;29;1S;375-576.

73. Laver KE, Schoene D, Crotty M, George S, Lannin NA, Sherrington C. Telerehabilitation services for stroke. Cochrane Database System Rev. 2013; 12 (CD010255). doi: 10.1002/14561858.CD010255.pub2.
74. Zheng C, Lynch L, Taylor N. Effect of computer therapy in aphasia: A systematic review. Aphasiology. 2016; 30(2-3):211-244. doi: 10.1080/02687038.2014.996521.
75. Meltzer JA, Baird AJ, Steele RD, Harvey SJ. Computer-based treatment of post-stroke language disorders: A non-inferiority study of telerehabilitation compared to in-service delivery. Aphasiology. 2018;32(3):290-311. doi: 10.1080/02687038.2017.1355440
76. Woolf C, Caute A, Haigh Z, Galliers J, Wilson S, Kessie A, Hirani S, et al. A comparison of remote therapy, face to face therapy and an attention control intervention for people with aphasia: A quasi-randomised controlled feasibility study. Clinical Rehabilitation. 2016;30(4):359-373. doi: 10.1177/0269215515582074
77. American Speech-Language-Hearing Association. Telepractice [Professional Issues]. Available from: www.asha.org/practice-portal.
78. Cassarly C, Matthews LJ, Simpson, AN, Dubno JR. The Revised Hearing Handicap Inventory and Screening Tool Based on Psychometric Reevaluation of the Hearing Hadnicap Inventories for the Elderly and Adults. Ear and Hearing. 2020; 21(1):95-105 doi: 10.1097/AUD.0000000000000746