Speech Therapy for Children with Childhood Apraxia of Speech (CAS): A Phase 1 Randomized Controlled Trial of ASSIST (Apraxia of Speech Systematic Integral Stimulation Treatment)

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STATEMENT OF COMPLIANCE

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

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

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

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

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator:

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Speech Therapy for Children with Childhood Apraxia of Speech (CAS): A Phase 1 Randomized Controlled Trial of ASSIST (*Apraxia of Speech Systematic Integral Stimulation Treatment*)

Grant Number: NIH R01 DC017768

Study Description: Childhood apraxia of speech (CAS) is a pediatric motor speech disorder that impairs the planning of movements needed for intelligible speech. Children with CAS often show little or slow progress in standard speech therapy. This research is a Phase 1 study that tests initial efficacy and optimal parameters of a theoretically based integral stimulation treatment called ASSIST (Apraxia of Speech Systematic Integral Stimulation Treatment).

In four small randomized group design studies ovr 3 recruitment cycles, children (N=20 per recruitment cycle) receive 16 hours of individual ASSIST. The four studies systematically investigate initial efficacy of ASSIST and effects of treatment intensity (ASSIST delivered over 2 vs. 4 weeks), practice complexity (simple vs. complex phonetic context) and lexicality (word vs. nonword targets). All three recruitment cycles are conducted in the context of a summer camp for children with CAS.

Each study also systematically examines the effect of treatment on functional outcome measures, including parent ratings of intelligibility and communicative participation, and objective intelligibility measures obtained from unfamiliar listeners.

Objectives:

Primary Objective:

(a) To test the initial efficacy of intensive ASSIST for children with CAS, by comparing short-term gains in speech accuracy with gains for children who have not (yet) received ASSIST. (Study 1)

Secondary Objectives:

(b) To determine optimal parameters of ASSIST with respect to practice COMPLEXITY (Simple vs. Complex practice) (Study 2)
(c) To determine optimal parameters of ASSIST with respect to target LEXICALITY (Words vs. Nonwords targets) (Study 3)
(d) To determine optimal parameters of ASSIST with respect to practice INTENSITY (Massed vs. Distributed practice) (Study 4)
(e) To determine changes on functional outcome measures following ASSIST with respect to caregiver-rated measures of intelligibility
(f) To determine changes on functional outcome measures following ASSIST with respect to caregiver-rated measures of communicative participation.
(g) To determine changes on functional outcome measures following ASSIST treatment with respect to objective intelligibility measures based on orthographic transcription by unfamiliar listeners.

Endpoints:

Primary Endpoint:

(a) *Perceptual accuracy of treated items* 1 week post treatment, judged by blinded data analysts from audio recordings.

Secondary Endpoints:

(a) (SE-1) *Perceptual accuracy of the full 30-item target set* 1 week post treatment, judged by blinded data analysts from audio recordings.
(b) (SE-2) *ICS Mean Score* 1 week post treatment: Caregiver rating of their child's intelligibility in context, using the Intelligibility-in-Context Scale (ICS; McLeod et al., 2012, 2015).
(c) (SE-3) *FOCUS-34 Mean* Score 1 week post treatment: Caregiver rating of their child's communicative participation, using the Focus on Outcomes of Communication Under Six (FOCUS-34; Thomas-Stonell et al., 2012) (25_ASSIST_FOCUS).
(d) (SE-4) *TOCS+ Intelligibility* 1 week post treatment: Percentage of words correctly understood from the audio recording by blinded unfamiliar listeners

Study Population:	60 children with childhood apraxia of speech (CAS), between 4 and 10 years old, any gender, with N=20 per recruitment cycle.
Phase or Stage:	Phase 1
Description of Sites/Facilities Enrolling Participants:	Single site, US only: Temple University (main campus) Speech-Language-Hearing Center (TUSLHC), a university clinic for graduate student training. This clinic includes individual speech therapy rooms as well as several larger rooms for group activities. A gated, shaded grassy field next to the building is available for non-treatment related camp activities.
Description of Study Intervention/Experimental Manipulation:	The intervention is a behavioral speech therapy called Apraxia of Speech Systematic Integral Stimulation Treatment (ASSIST). Children receive 32 individual sessions of 30 minutes (16 hours total), in which the child works with a speech-language pathology (SLP) graduate student clinician on individualized speech goals. Practice involves multimodal cueing and feedback from the clinician, and practice conditions (e.g., elicitation method) are systematically adapted to the child's performance. Speech goals are words or phrases tailored to each child based on pre-treatment testing and personal relevance (note: Half the children in Study 3 [Recruitment Cycle 2] practice nonwords). *Targets* are practiced embedded in carrier phrases called *frames* (target + frame = *utterance*). The 16 hours of ASSIST are delivered individually, in person, over a period of 2 weeks (i.e. 4 sessions = 2 hours/day) in all 3 studies except Study 4 (Recruitment Cycle 3), in which half of the children receive the 16 hours over a period of 4 weeks (i.e. 2 sessions = 1 hour/day).
Study Duration:	48 months (4 years) from when the study opens to enrollment to completion of data collection.
Participant Duration:	5 months, including 2 weeks of evaluation up to 3 months prior to summer camp, plus 1.5 months (7 weeks) for the summer camp and data collection.

1.2 SCHEMA

Below is an overview of the design of the four RCTs in this study in relation to the three recruitment cycles. The dashed box indicates the primary study (Study 1: ASSIST vs. Delayed Control, combined across Cycles 1 and 2). The other studies are completed within a single cycle: Study 2 (Complexity) in Cycle 1, Study 3 (Lexicality) in Cycle 2, and Study 4 (Intensity) in Cycle 3.

Cycle 1 (Summer 1): **COMPLEXITY** (simple vs. complex real words).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Immediate ASSIST	*Simple*	T1	*8 hrs*	*8 hrs*	T2			T3
	Complex		8 hrs	8 hrs				
Delayed ASSIST	*Simple*					*8 hrs*	*8 hrs*	
	Complex					8 hrs	8 hrs	

Cycle 2 (Summer 2): **LEXICALITY** (words vs. nonwords).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Immediate ASSIST	*Real*	T1	*8 hrs*	*8 hrs*	T2			T3
	Nonsense		8 hrs	8 hrs				
Delayed ASSIST	*Real*					*8 hrs*	*8 hrs*	
	Nonsense					8 hrs	8 hrs	

Cycle 3 (Summer 3): **INTENSITY** (massed vs. distributed treatment).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Massed ASSIST	*Immediate*	T1	*8 hrs*	*8 hrs*	T2			T3
	Delayed					*8 hrs*	*8 hrs*	
Distributed ASSIST	Distributed		4 hrs	4hrs		4 hrs	4 hrs	

STUDY 1 (Primary Objective): ASSIST vs. Delayed Control

Data from Cycles 1 and 2 will be combined (shown in the pink dashed box). Groups (ASSIST, Delayed Control) will be compared at T2.

STUDY 2 (Complexity)

Data from Cycle 1 will be combined across Immediate and Delayed ASSIST. Groups (Simple, Complex) will be compared post treatment. For Immediate ASSIST, pre = T1 and post = T2; for Delayed ASSIST, pre = T2 and post = T3.

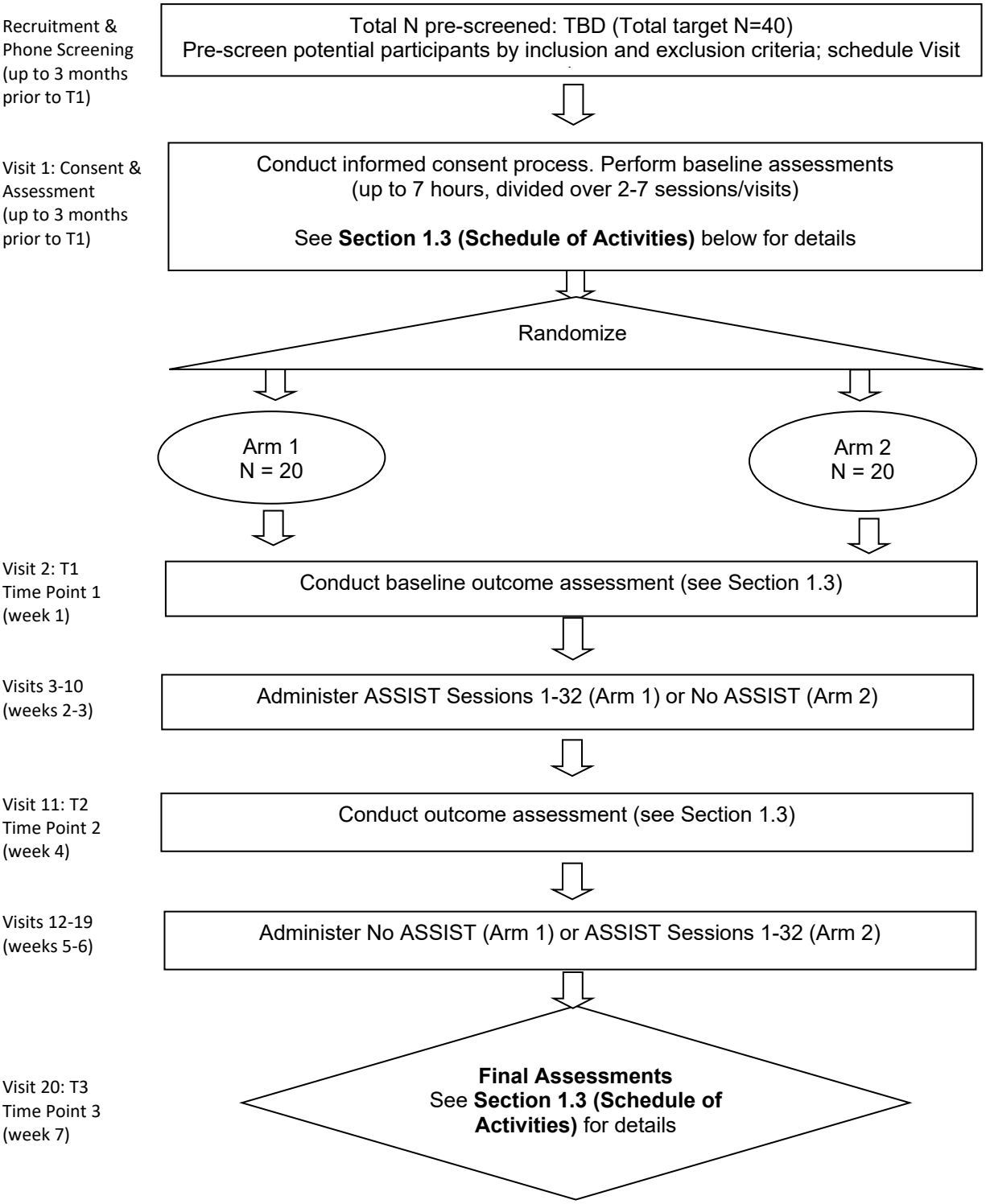
STUDY 3 (Lexicality)

Data from Cycle 2 will be combined across Immediate and Delayed ASSIST. Groups (Word, Nonword) will be compared post treatment. For Immediate ASSIST, pre = T1 and post = T2; for Delayed ASSIST, pre = T2 and post = T3.

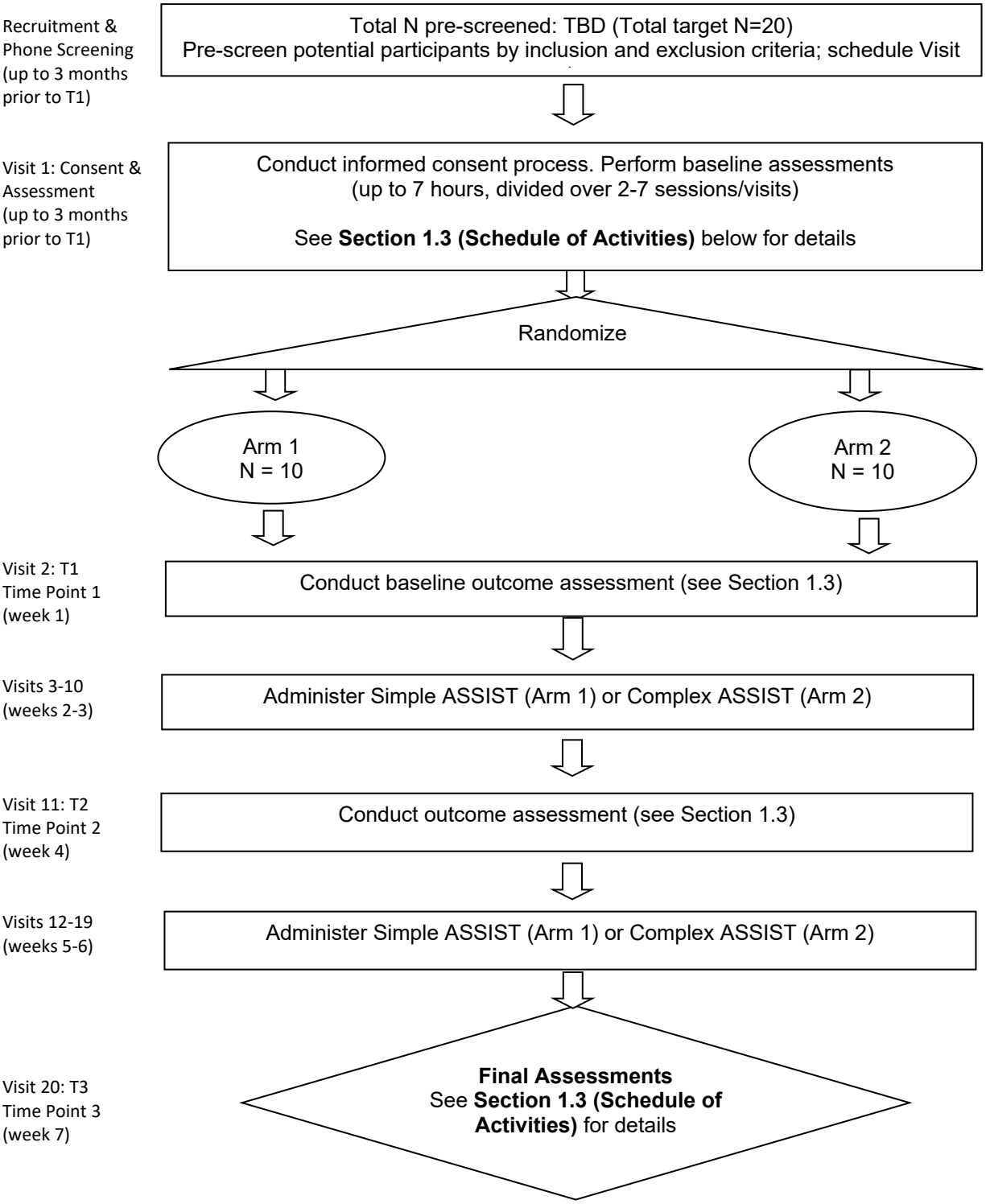
STUDY 4 (Intensity)

Data from Cycle 3 will be used to compare groups (Massed, Distributed) at T3. For Massed ASSIST, data will be combined across Immediate and Delayed Massed ASSIST conditions.

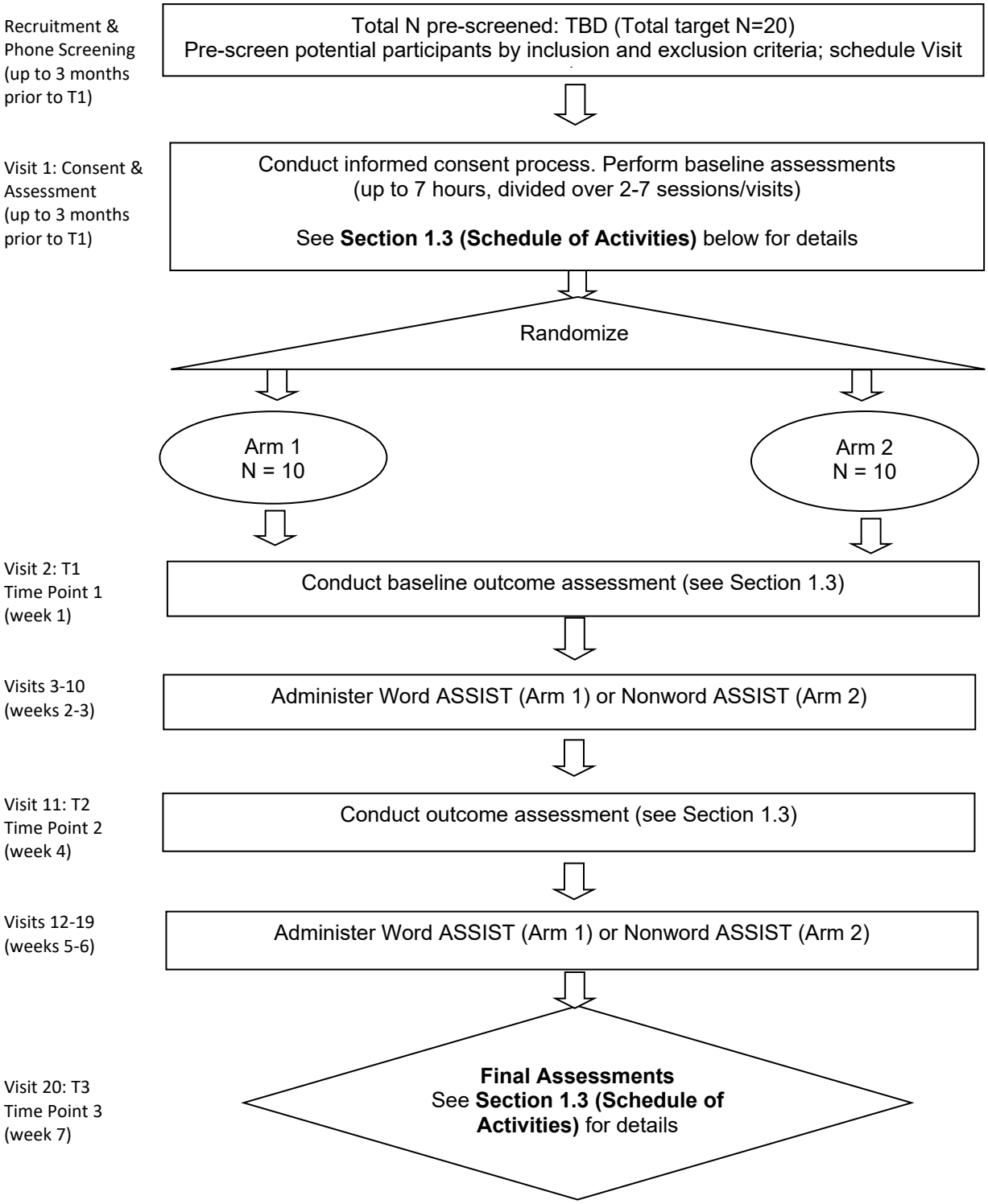
<u>Study 1</u> Flow: <u>ASSIST</u> vs. No ASSIST. Combined across two Recruitment Cycles (Cycle 1 and Cycle 2)



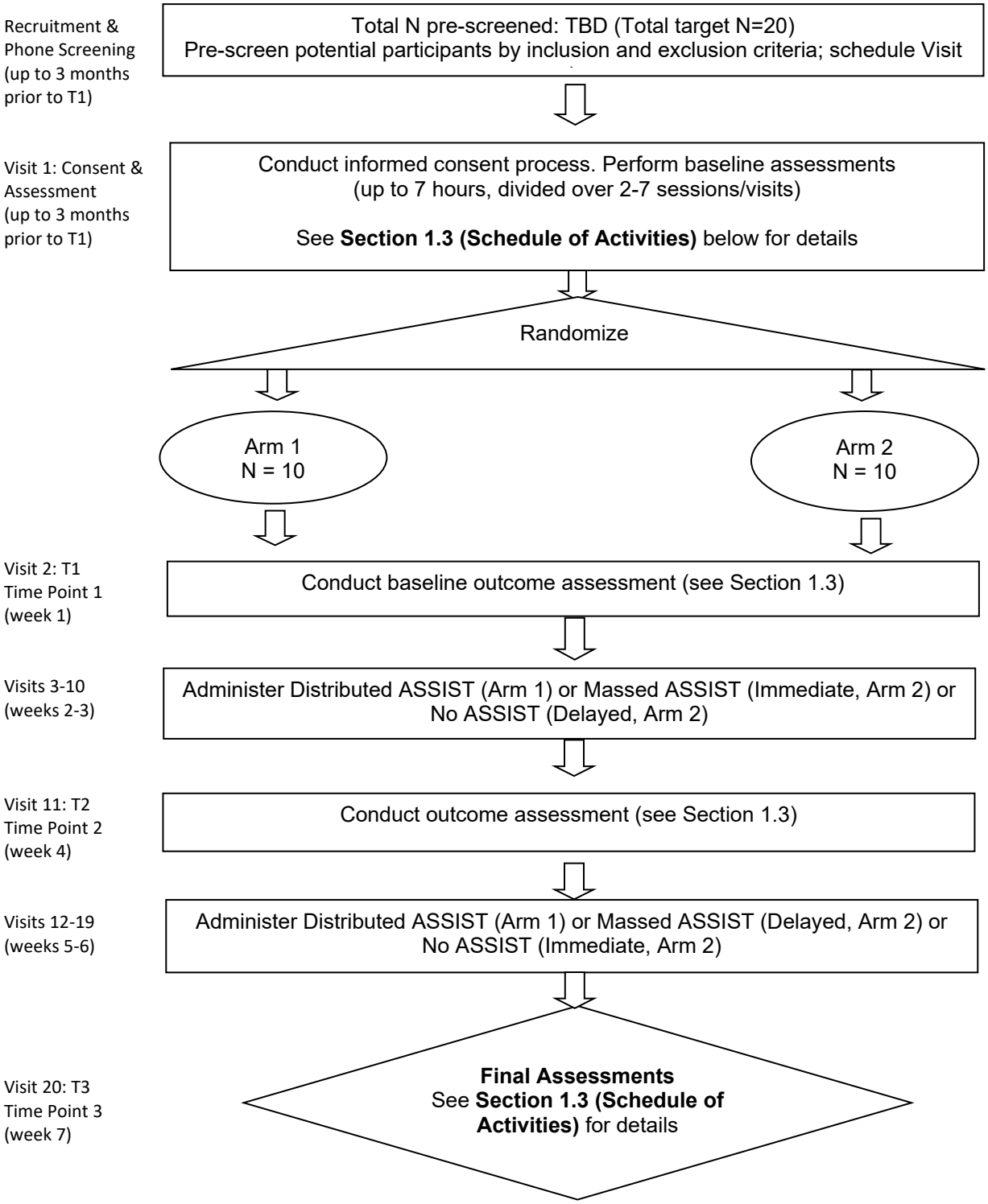
<u>Study 2</u> Flow: Simple ASSIST vs. Complex ASSIST). Cycle 1, combined across Immediate and Delayed.



<u>Study</u> 3 Flow: Word ASSIST vs. Nonword ASSIST. Cycle 2, combined across Immediate and Delayed.



<u>Study 4</u> Flow: Massed ASSIST vs. Distributed ASSIST. Cycle 3.



1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 (up to 3 months before T1)	Visit 2: T1 (week 1)	Visits 3-10 (weeks 2-3)	Visit 11: T2 (week 4)	Visits 12-19 (weeks 5-6)	Visit 20: T3 (week 7)
Recruitment & Phone Screening	X						
Informed Consent		X					
Demographics		X					
Clinical history		X					
Target Selection Questionnaire		X					
SLP diagnosis from 3 SLPs (CAS3SLP)		X					
DEMSS		X					
MaxPT		X					
GFTA		X					
DEAP		X					
SRT		X					
RIAS		X					
OME		X					
Hearing		X					
PPVT		X					
EVT		X					
CELF		X					
CTOPP		X					
Randomization (after final sample has been determined, before T1)		X					
Outcome Evaluation							
Target Repetition Task			X		X		X
TOCS+ Intelligibility			X		X		X
ICS			X		X		X
FOCUS-34			X		X		X
ASSIST or No ASSIST (Delayed Treatment Control group)				X		X	
Adverse Events Reporting (FRS)			X	X	X	X	X

ASSIST = Apraxia of Speech Systematic Integral Stimulation Treatment
CELF = Clinical Evaluation of Language Fundamentals (Semel et al., 2004)
CTOPP = Comprehensive Test of Phonological Processing (Wagner et al., 1999)
DEAP = Diagnostic Evaluation of Articulation and Phonology [Word Inconsistency] (Dodd et al., 2006)
DEMSS = Dynamic Evaluation of Motor Speech Skill (Strand et al., 2013)
EVT = Expressive Vocabulary Test (Williams, 2007)
FOCUS-34 = Focus on Outcomes of Communication Under Six (Thomas-Stonell et al., 2012, 2013a,b)
FRS = Frustration Rating Scale

GFTA = Goldman-Fristoe Test of Articulation (Goldman & Fristoe, 2015)
Hearing = Hearing screen (ASHA, 1997)
ICS = Intelligibility-in-Context Scale (McLeod et al., 2012, 2015)
MaxPT = Maximum Performance Task protocol (Thoonen et al., 1996, 1999)
OME = Oral mechanism examination (Robbins & Klee, 1987)
PPVT = Peabody Picture Vocabulary Test (Dunn & Dunn, 2007)
RIAS = Reynolds Intellectual Assessment Scales [nonverbal subtests] (Reynolds & Kamphaus, 2018)
SRT = Syllable Repetition Task (Shriberg et al., 2009).
TOCS+ = Test of Children's Speech Intelligibility tests (Hodge et al., 2009)

2 INTRODUCTION

2.1 STUDY RATIONALE

Childhood apraxia of speech (CAS) is a pediatric motor speech disorder that impairs the planning of movements needed for intelligible speech. CAS may limit literacy, academic and economic outcomes and participation in society. Various treatment approaches exist, yet the current evidence base is limited both in study quality and scope. In terms of study quality, all studies to date have involved single-subject designs with small sample sizes. In terms of scope, the extant studies vary considerably with respect to target types and treatment intensity. Another limitation of scope is that virtually all studies have relied exclusively on impairment-level outcome measures, and have not included functional outcome measures related to activity and participation. For these reasons, speech-language pathologists lack adequate information to make clinical decisions for their clients.

This Phase 1 study tests initial efficacy and optimal parameters of a theoretically based integral stimulation treatment called **ASSIST** (Apraxia of Speech Systematic Integral Stimulation Treatment). ASSIST targets the Body Functions level of the World Health Organization's International Classification of Functioning and Disability (Child & Youth version; WHO ICF; WHO, 2007), specifically the impaired function of *speech motor planning*, as measured via perceptually-determined speech accuracy of treated targets (primary outcome). In three small randomized group design studies, children with CAS receive individual ASSIST to systematically investigate treatment intensity, target complexity, and target lexicality. These studies will be implemented in the format of a summer camp. For each study, we will also examine the effect of treatment on functional outcome measures, including parent ratings of intelligibility and communicative participation, and objective intelligibility measures obtained from unfamiliar listeners. Thus, this research will contribute high-quality evidence that will help speech-language pathologists make evidence-based clinical decisions. The long term goal is to develop optimally effective treatments to maximize outcomes and communicative quality of life for the many children with CAS and their families.

2.2 BACKGROUND

Childhood apraxia of speech (CAS) is a pediatric motor speech disorder that impairs the planning of movements needed for intelligible speech. CAS may limit literacy, academic and economic outcomes and participation in society. Prevalence of CAS is estimated at 1 to 13 per 1,000 children. With ~40 million children under 10 in the US, these estimates translate to between 40,000 and 520,000 children with CAS. Over 60% of school-based speech-language pathologists report having children with CAS on their caseload, with on average 3 children per caseload. Children with CAS often show little or slow progress in standard therapy, which has led to recommendations for intensive intervention and calls for systematic research to optimize outcomes. Given the limited resources in clinical settings, it is imperative to maximize impact of these limited resources for children with CAS. Various treatments for CAS exist, with integral stimulation treatments having received the most replicated support to date. Integral stimulation treatments involve multimodal input supports to elicit speech targets ("watch me, listen to me, say what I say"). Any treatment for CAS must specify both the *what* and the *how*. The *what* relates to which targets are being practiced (sounds, syllables, words, phrases, etc.) The *how* relates to the treatment techniques and procedures applied to those targets (e.g., feedback, cues, order in which targets are practiced). This trial addresses both of these core questions in treatment for CAS.

The current evidence base for CAS treatment is limited in that it leaves several critical clinical questions unanswered. First, the efficacy of treatment has only been addressed using single-case experimental designs with relatively small samples sizes. Second, treatment targets vary in complexity across studies, which likely influenced the treatment response. Third, all integral stimulation treatment studies used real word targets but reported little to no generalization to untrained words; in contrast, other approaches targeting nonwords show generalization to untrained words. Fourth, treatment intensity has varied widely across integral stimulation treatment studies, so that optimal intensity remains unknown. Finally, outcome measures have exclusively focused on impairment (speech accuracy), not on more functional outcomes (e.g., intelligibility, participation).

2.2.1 EFFICACY OF ASSIST

ASSIST uses integral stimulation methods to elicit and support children's productions, slow rate and cues to improve speech movements, and systematically works toward independent (non-imitated) production by fading cues. Because CAS is a speech motor planning disorder, ASSIST focuses on speech movements and incorporates principles of motor learning, which indicate practice conditions that maximize learning. ASSIST includes a pre-practice and a practice component. The goal of pre-practice is to prepare the child for learning by fostering motivation, explaining activities in relation to goals, and establishing target movements with maximal supports. The goal of practice is to practice the movements many times to strengthen the speech motor plans. Another core element of ASSIST is an integral focus on prosody, because abnormal prosody is a core feature of CAS. A focus on prosody may also benefit segmental accuracy. For this reason, targets are practiced embedded in a phrase (e.g., 'my *doll*'). The primary purpose of this research is to determine initial efficacy of ASSIST.

2.2.2 TARGET COMPLEXITY

One factor that has varied between studies and for which plausible competing hypotheses exist is target complexity. The critical question is whether children with CAS benefit more from a focus on simple or complex targets.

According to the ***Simplicity Hypothesis***, children with CAS learn more effectively with simple targets, typically sounds that the child can already produce or are typically acquired early, and simple syllable shapes (e.g., consonant-vowel [CV] syllables such as me, hi). The rationale is that simpler sounds and syllables foster early success and enable the child to build longer, more complex movement plans by combining basic building blocks. The Simplicity Hypothesis reflects standard clinical practice for CAS.

In contrast, the ***Complexity Hypothesis*** claims that children with CAS learn more effectively with complex targets, typically sounds the child cannot yet produce or that are acquired late in typical development, and complex syllables (e.g., CVCCVC [bathroom]). The rationale is that complex targets provide more practice with integrating and sequencing movement components, allowing children to extract more information about the underlying speech motor skill; complex targets also may subsume simpler movements which therefore receive practice as well. Benefits of complex targets for learning have been shown across domains and populations, including adults with apraxia of speech and children with speech disorders.

2.2.3 TARGET LEXICALITY

Most treatment approaches for CAS focus on real-word targets, but some target nonwords. The critical question is whether children with CAS benefit more from a focus on word or nonword targets.

According to the ***Word Hypothesis***, children with CAS learn more effectively with existing words than with nonwords. The rationale is that real words enhance motivation due to their communicative relevance; real words may also receive practice outside the treatment setting. The focus of such treatments is typically to increase accuracy and consistency of important functional vocabulary. The Word Hypothesis represents standard clinical practice for children with CAS.

In contrast, the ***Nonword Hypothesis*** claims that children with CAS learn more effectively with nonwords. The rationale is that nonwords require activating and assembling novel motor plans, instead of relying on retrieving pre-existing, possibly incorrect speech motor plans and semantic activation; nonwords also allow for more systematic and controlled variation of phonetic context.

2.2.4 TREATMENT INTENSITY

Intensity is defined here not as overall amount of treatment but as amount of treatment over a given time period (also referred to as treatment distribution). Despite its presumed importance, treatment

distribution has received little systematic study in treatment for CAS. The critical question is whether children with CAS benefit more from massed or distributed treatment, if treatment amount is equal.

According to the ***Distributed Hypothesis***, children with CAS learn more effectively with distributed than with massed treatment. This hypothesis stems from the motor- and verbal learning literatures, both of which show superior learning for distributed compared to massed practice. Since CAS is a motor planning disorder that affects a verbal skill, the Distributed Hypothesis is a priori plausible.

In contrast, the ***Massed Hypothesis*** states that children with CAS learn more effectively with massed than with distributed treatment. This hypothesis is based on the neuroplasticity literature. According to this hypothesis, massed practice facilitates neuroplastic processes (e.g., synaptogenesis) which in turn support sustained behavioral performance improvements (i.e. learning). Most of this literature is based on animal models of neurological lesions, although there has been application to human rehabilitation. However, these studies often conflate amount and distribution, obscuring effects of distribution.

2.2.5 FUNCTIONAL OUTCOME MEASURES

To date, outcome measures have mostly been limited to impairment-level measures (accuracy of sounds or words) rather than functional outcome measures of activity and participation. In the few studies that included functional outcome measures, all participants received treatment, making it impossible to discern treatment effects. This research will determine effects of speech treatment on functional outcome measures for CAS. We expect that children receiving ASSIST will show greater gains on these outcome measures than children in the control group. These results will provide critical information to speech-language pathologists.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

For children, the standardized tests, assessment procedures, and experimental treatment are not known to be associated with increased risk. Children may experience temporary frustration, boredom, or fatigue during assessment, treatment, or data collection procedures. Risks associated with outdoor activities include weather-related risk, transportation-related risk, and location-related risk. Weather-related risk includes getting wet from rain or getting a sun burn. Transportation-related risk includes getting lost and traffic. Location-related risk includes potential hazardous materials on the site (e.g., glass) or insect bites or stings. There is also always a possibility of loss of confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

Although this is a treatment study, and we expect children to improve their speech skills, we cannot guarantee such benefits to the children. Children may also receive a benefit from participating in group activities with other children with CAS because such activities provide social support and opportunities for vicarious learning of communicative strategies. Parents may gain a better understanding of their child's speech and language abilities as revealed through testing. We provide parents with a report of the test results, which may aid in educational or clinical planning for the children. (These reports will state clearly that the evaluation is performed for research purposes and is not intended for clinical purposes beyond the study.)

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

For children, the risk of temporary frustration, boredom, or fatigue during assessment, treatment, or data collection procedures is mitigated as follows. Breaks are offered throughout all sessions, and assessment sessions may be discontinued and rescheduled for continuation at a later date. During treatment, targets are selected that are personally relevant and/or engaging. The treatment procedures are designed to be adaptive to children's performance as a way to minimize frustration. Treatment sessions are kept to no more than 30 minutes, and include frequent brief breaks.

Risks associated with outdoor activities are mitigated as follows.

- To mitigate weather-related risk (e.g., getting wet from rain; getting a sun burn), we do not go outside when it rains, and the close proximity to the clinic ensures that the children will be inside quickly in the case of unexpected rain. We ask parents to provide clothing appropriate for the weather (e.g., coat, sun hat). With respect to sun exposure, the site was selected in part because it has large trees that provide shade. We also ask parents to provide an appropriate sunscreen for their child and seek parents' permission to apply sunscreen to their children.
- To mitigate transportation-related risk (e.g., getting lost), the area is very close to the clinic (~100 feet), and does not involve crossing any street nor walking along a street. We have a Child:Adult ratio of 2:1 to escort children to the site, to prevent children from getting lost.
- To mitigate location-related risk (e.g., hazardous materials on the site; insect bites), we inspect the site and clean up as needed each day before taking the children outside. In addition, the Associate Director of Grounds Operations of Temple University will ensure a thorough inspection prior to the start of camp and removal of dangerous items (e.g., trim weak tree limbs) and inspect the site regularly during camp weeks. We also have an emergency medical kit on site in case of scrapes or insect stings or bites, and ask parents' permission to administer minor medical care (e.g., applying Band-Aids, wound cream). For children who have allergies, we will ask parents to provide appropriate medical resources (e.g., inhaler).

To mitigate risk of loss of confidentiality, we follow the procedures described in ***Section 10.1.3, Confidentiality and Privacy***. Briefly, participants will be assigned a unique ID code; only the Investigator

and appropriate research personnel will have access to the master list linking names and ID codes on an as-needed basis. Paper files are stored in locked file cabinets accessible only to approved research personnel, and electronic data are stored in a HIPAA-compliant server accessible only via password-protected computers. Any identifiable data will be accessible only to qualified research personnel for research purposes and will not be shared with others, unless participants or parents provide explicit written permission to share this information (for example, to share with clinical service providers), or as required by law or federal, state, or other appropriate regulatory agencies.

Children will be tested and receive treatment individually. However, because the study is conducted in the format of a camp, children and parents will interact with other children and parents. Study staff will use names for pragmatic reasons, but will share no other identifying with other children or parents.

Parents are informed of all these procedures, both in person (verbally) and in writing on the Parent Informed Consent Form. They are informed that they may change their mind or revoke authorizations in writing at any time (e-mail accepted). Further, parents and children are told that they may choose to not answer any questions that they do not feel comfortable answering.

Given the minimal risks and the risk-mitigation strategies described above, and the significant gap in knowledge and lack of well-established evidence-based interventions for CAS, the minimal risks noted are considered acceptable. The potential benefits of this research (first-ever RCT level evidence of integral stimulation treatment for CAS) outweigh these minimal risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To test initial efficacy of intensive ASSIST	(1) Perceptual accuracy of *treated* targets 1 week post treatment (2) Perceptual accuracy of full set of targets 1 week post treatment Greater change score in the ASSIST group than in the no-ASSIST group at T2 (t-test, α=.05, 2-tailed)	Perceptual accuracy reflects speech motor planning skills, the presumed underlying impairment in CAS.	ASSIST targets speech motor planning skills, which is expected to improve perceptual accuracy of speech.
Secondary			
To optimize ASSIST: To compare Simple vs. Complex practice	(1) Perceptual accuracy of *treated* targets 1 week post treatment (2) Perceptual accuracy of full set of targets 1 week post treatment Greater change score in the Simple or Complex ASSIST group pre to post (t-test, α=.05, 2-tailed)	Perceptual accuracy reflects speech motor planning skills, the presumed underlying impairment in CAS.	Simple practice establishes building blocks, fosters success Complex practice provides more practice integrating and sequencing movements

OBJECTIVES	**ENDPOINTS**	**JUSTIFICATION FOR ENDPOINTS**	**PUTATIVE MECHANISMS OF ACTION**
To optimize ASSIST: To compare Word vs. Nonword targets	(1) Perceptual accuracy of ***treated*** targets 1 week post treatment (2) Perceptual accuracy of full set of targets 1 week post treatment Greater change score in the Word or Nonword ASSIST group pre to post (t-test, α=.05, 2-tailed)	Perceptual accuracy reflects speech motor planning skills, the presumed underlying impairment in CAS.	Word targets enhance learning via increased motivation due to functional relevance and practice outside treatment Nonword targets enhance learning through focus on underlying speech motor skill of assembling motor plans (vs. retrieving existing speech motor plans)
To optimize ASSIST: To compare Massed vs. Distributed practice	(1) Perceptual accuracy of ***treated*** targets 1 week post treatment (2) Perceptual accuracy of full set of targets 1 week post treatment Greater change score in the Massed or Distributed ASSIST group at T3 (t-test, α=.05, 2-tailed)	Perceptual accuracy reflects speech motor planning skills, the presumed underlying impairment in CAS.	Massed practice facilitates neuroplasticity (reported to be optimal in neuroplasticity literature and the few studies with CAS and other pediatric speech sound disorders) Distributed practice results in more forgetting, and requires deeper processing for the next attempt (reconstructing the movement from scratch), resulting in more detailed movement plans
To determine effects of ASSIST on distal outcome measures	ICS Greater change score in the ASSIST group than in the no-ASSIST group at T2 (t-test, α=.05, 2-tailed)	ICS reflects caregiver-reported perception of the effectiveness of everyday speech communication of their child.	Improved speech motor planning skills lead to increased speech accuracy, which increases intelligibility in everyday contexts.
To determine effects of ASSIST on distal outcome measures	FOCUS-34 Greater change score in the ASSIST group than in the no-ASSIST group at T2 (t-test, α=.05, 2-tailed)	FOCUS reflects caregiver-reported perception of the communicative function of their child in everyday life.	Increased speech accuracy and intelligibility facilitates everyday communication interactions and communicative confidence.
To determine effects of ASSIST on distal outcome measures	TOCS+ Intelligibility Greater change score in the ASSIST group than in the no-ASSIST group at T2 (t-test, α=.05, 2-tailed)	TOCS+ reflects gold-standard measure of speech intelligibility	Improved speech motor planning skills lead to increased speech accuracy, which increases intelligibility.
Tertiary/Exploratory			
To evaluate safety of ASSIST	Clinician-rated child frustration level (FRS)	FRS: Acts as a safety mechanism, to avoid unnecessary treatment-related frustration (stopping rule based on FRS)	Intensive speech therapy, with many repeated failures and corrective feedback, could increase child frustration levels.

4 STUDY DESIGN

4.1 OVERALL DESIGN

4.1.1 OVERVIEW

Below is a reminder of the design of the four RCTs in this study (3 cycles plus 1 study combined across Cycles 1 and 2). Dashed box indicates the primary study (Study 1: ASSIST vs. Delayed Control).

Cycle 1 (Summer 1): **COMPLEXITY** (simple vs. complex real words).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Immediate ASSIST	*Simple*	T1	*8 hrs*	*8 hrs*	T2			T3
	Complex		8 hrs	8 hrs				
Delayed ASSIST	*Simple*					*8 hrs*	*8 hrs*	
	Complex					8 hrs	8 hrs	

Cycle 2 (Summer 2): **LEXICALITY** (words vs. nonwords).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Immediate ASSIST	*Real*	T1	*8 hrs*	*8 hrs*	T2			T3
	Nonsense		8 hrs	8 hrs				
Delayed ASSIST	*Real*					*8 hrs*	*8 hrs*	
	Nonsense					8 hrs	8 hrs	

Cycle 3 (Summer 3): **INTENSITY** (massed vs. distributed treatment).

Group	Condition	wk1	wk2	wk3	wk4	wk5	wk6	wk7
Massed ASSIST	*Immediate*	T1	*8 hrs*	*8 hrs*	T2			T3
	Delayed					*8 hrs*	*8 hrs*	
Distributed ASSIST	Distributed		4 hrs	4hrs		4 hrs	4 hrs	

Given the interwoven design (see ***Section 1.2, Schema,*** figure repeated above), in both Cycles 1 and 2, children are allocated with equal probability to one of four groups (Immediate Simple/Word, Immediate Complex/Nonword, Delayed Simple/Word, Delayed Complex/Nonword) (5:5:5:5). In Cycle 3, children are allocated to one of 3 groups (Distributed vs. Massed Immediate vs. Massed Delayed) to such that children have equal probability to receive Massed or Distributed ASSIST (5:5:10).

4.1.2 COMMON ELEMENTS

4.1.2.1 RANDOMIZATION

Randomization is determined by an investigator not involved in assessment or intervention (biostatistician). Children are randomly allocated to conditions via permuted block randomization (block

size 4) within each recruitment cycle, to maximize equivalent group sizes across phases and conditions. The biostatistician sends the randomization sequence (a series of letters ABCD in random order) to a research assistant not otherwise involved in the study, who assigns a particular phase (Immediate or Delayed) + condition (Simple/Complex, Word/Nonword) combination to each letter and creates serially numbered sealed opaque envelopes with the randomization sequence. Group assignment is concealed from any personnel involved in child and caregiver interactions until after assessment and target selection is complete. Allocation is revealed for all children in a lab meeting with at least three team members present to avoid errors.

4.1.2.2 INTERVENTION

All children receive 16 hours (32 sessions of 30 minutes) of ASSIST, across 4 sessions per day, 4 days per week for 2 weeks (either the first two weeks or the second two weeks). All children are tested 1 week before treatment (T1), after 2 weeks (T2), and post treatment (T3). The critical comparison is at T2 for Study 1 (ASSIST vs. No ASSIST), at T3 for Study 4 (Massed vs. Distributed ASSIST), and post treatment (T2 or T3) for Studies 2 and 3 (Simple vs. Complex and Word vs. Nonword ASSIST).

ASSIST (Apraxia of Speech Systematic Integral Stimulation Treatment) is a theoretically grounded and clinically informed speech therapy intervention for CAS. ASSIST involves repeated structured practice of meaningful words and phrases with cueing and feedback. It incorporates principles of motor learning and systematically adapts difficulty and introduces new targets based on a child's performance. Targets are embedded in carrier phrases (frames).

4.1.3 STUDY-SPECIFIC HYPOTHESES AND ENDPOINTS

4.1.3.1 STUDY 1: ASSIST VS. NO (DELAYED) ASSIST

Study 1 is a single-site Phase 1 randomized clinical trial using a prospective outcome-assessor-blinded two-arm delayed control group (cross-over) design. The critical outcome assessment point is 1-week post treatment for the Immediate ASSIST group (T2).

> *ASSIST Hypothesis*: ASSIST improves speech motor planning skills in CAS. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive ASSIST than children who do not receive ASSIST.

4.1.3.2 STUDY 2: SIMPLE ASSIST VS. COMPLEX ASSIST

Study 2 is a single-site Phase 1 randomized clinical trial using a prospective outcome-assessor-blinded two-arm group design. The critical outcome assessment point is 1-week post treatment (either T2 or T3, depending on the Immediate or Delayed allocation).

Simple ASSIST involves ASSIST (see above) in which the frames (carrier phrases) are simple, as defined by an Index of Phonetic Complexity (IPC) value of 0-2. Complex ASSIST involves ASSIST in which the frames are complex, as defined by an IPC value of 3-5.

Simplicity Hypothesis: Children with CAS learn more effectively with simple targets. Simpler sounds and syllables foster early success and enable the child to build longer, more complex movement plans by combining basic building blocks. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Simple ASSIST than children who receive Complex ASSIST.

Complexity Hypothesis: Children with CAS learn more effectively with complex targets. Complex targets provide more practice with integrating and sequencing movement components, allowing children to extract more information about the underlying speech motor skill; complex targets also may subsume simpler movements which therefore receive practice as well. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Complex ASSIST than children who receive Simple ASSIST.

4.1.3.3 STUDY 3: WORD ASSIST VS. NONWORD ASSIST

Study 3 is a single-site Phase 1 randomized clinical trial using a prospective outcome-assessor-blinded two-arm group design. The critical outcome assessment point is 1-week post treatment (either T2 or T3, depending on the Immediate or Delayed allocation).

Word ASSIST involves ASSIST (see above) in which the targets are real words, selected based on personal functional relevance. Nonword ASSIST involves ASSIST in which the targets are nonwords, created by changing a stressed vowel and 0 or more other sounds in the personally relevant real words.

Word Hypothesis: Children with CAS learn more effectively with existing words than with nonwords. Real words enhance motivation due to their communicative relevance; real words may also receive practice outside the treatment setting. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Word ASSIST than children who receive Nonword ASSIST.

Nonword Hypothesis: Children with CAS learn more effectively with nonwords. Nonwords require activating and assembling novel motor plans, instead of relying on retrieving pre-existing, possibly incorrect speech motor plans and semantic activation; nonwords also allow for more systematic and controlled variation of phonetic context. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Nonword ASSIST than children who receive Word ASSIST.

4.1.3.4 STUDY 4: MASSED ASSIST VS. DISTRIBUTED ASSIST

Study 4 is a single-site Phase 1 randomized clinical trial using an outcome-assessor-blinded two-arm group design. The critical outcome assessment point is at T3.

Randomization involves permuted block-randomization with a block size of 4 to ensure equal sample sizes. Two of the block elements will indicate assignment to Distributed ASSIST (see *Section 1.2, Schema*). Children are allocated with equal probability to one of four groups (Immediate Massed, Delayed Massed, Distributed 1, Distributed 2) (5:5:5:5).

ASSIST is as above (complexity and lexicality to be determined by optimal outcomes in Studies 2 and 3) but delivered either over 2 weeks (Massed) or 4 weeks (Distributed).

> *Distributed Hypothesis*: Children with CAS learn more effectively with distributed than with massed treatment. Distributed practice results in more forgetting, and requires more, deeper processing for the next attempt (reconstructing the movement from scratch), resulting in more detailed movement plans. This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Nonword ASSIST than children who receive Word ASSIST
>
> *Massed Hypothesis*: Children with CAS learn more effectively with massed than with distributed treatment. Massed practice facilitates neuroplastic processes (e.g., synaptogenesis) which in turn support sustained behavioral performance improvements (i.e. learning). This hypothesis predicts a greater increase in perceptual speech accuracy at 1 week post treatment for children who receive Nonword ASSIST than children who receive Word ASSIST.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study design was selected for several reasons.

First, to establish experimental control against a no-treatment condition (the Delayed ASSIST group). As a first examination of ASSIST, a Phase 1 study against a no-treatment comparison is appropriate to establish that the intervention is better than absence of intervention.

Second, to enable examination of effects on distal outcome measures, which requires a group comparison design (vs. a within-participant or within-group design). As one of the first studies of CAS treatment to consider such distal outcomes (e.g., caregiver-rated communicative function), a group design is appropriate to evaluate distal effects and generate effect size data to power future trials on more meaningful distal outcome measures.

Third, randomizing children to different conditions (Complexity, Lexicality) within the Immediate and Delayed groups (using the same basic design and same procedures in Cycles 1 and 2) enables efficient evaluation of the “How” of ASSIST (procedures, techniques) and the “What” of ASSIST (targets). This yields both an assessment of the robustness of ASSIST (effect across conditions) and information to inform optimal parameters of ASSIST.

Fourth, to mitigate ethical concerns about withholding treatment from some children. By using a delayed control group design, all children receive the 16 hours of ASSIST, with the only difference in whether they receive ASSIST in the first or second two-week period.

Fifth, the intensive intervention period and study design facilitate recruitment and retention and a representative sample by lowering barriers to participation, and is also motivated by evidence suggesting intensive intervention is more effective for children with CAS.

4.3 JUSTIFICATION FOR INTERVENTION

CAS affects speech communication and thus participation in life, because virtually all social activities depend on speech communication. Children with CAS are at elevated risk for reading and academic challenges, reduced communicative participation, and reduced psychosocial well-being. These effects are long-term. Treatment progress is often slow for CAS, and intensive motor-focused treatment is recommended. Effective treatment for CAS has the potential to improve not only speech communication but also more distal outcomes, such as communicative participation.

ASSIST is delivered over 32 sessions for a total of 16 hours over 4 weeks (Study 4, Distributed group) or 2 weeks (all other groups). The amount is comparable to previous studies with other treatment approaches. ASSIST is delivered individually in a pull-out model in the context of a day camp setting. This context was chosen to minimize missed sessions and to provide a naturalistic supportive social environment. If at least 14 sessions (7 hours) are available, data are evaluable. All data are valuable given the current lack of RCT level evidence for integral stimulation treatments for CAS.

4.4 END-OF-STUDY DEFINITION

Children are considered to have completed the study if they have completed the evaluation, baseline assessment (T1), at least 14 intervention sessions, and Week 4 (T2) and Week 7 (T3) assessments.

The end of the study is defined as completion by all children of the Week 7 (T3) assessments shown in the Schedule of Activities (SOA), **Section 1.3**.]

5 STUDY POPULATION

This research includes children in the age range 4;0 to 9;11 (years;months) because the purpose of the research is to gain information about the initial efficacy and optimal parameters of a treatment for childhood apraxia of speech (a pediatric speech disorder). Children younger than 4;0 are excluded due to the attentional demands required for the proposed treatment. To date, all studies on integral stimulation treatment methods for CAS have included children 4;0 and older.

For this first Phase 1 clinical trial of ASSIST, the target population is from a relatively narrow spectrum, limiting the age range and type and number of comorbidities, in order to detect an initial effect of ASSIST for CAS. The age range also considers the summer camp setting in order to plan and facilitate group activities that are age-appropriate and of interest to the children.

Families complete a pre-screening upon initial contact by e-mail or phone to determine initial eligibility and, if eligible, to schedule the first in-person visit for screening. Pre-screening questions include verification of age, concomitant exclusionary diagnoses, ability to separate from family and toilet independently. For any children who are not eligible based on information provided during this pre-screening process, we explain the reason for their exclusion to them and thank them for their interest and time. Pre-screening also includes providing further information about the study and answering parent questions, and determining continued interest to participate if eligible.

During screening, children are evaluated to determine eligibility to *'participate'* (i.e. proceed with intervention and outcome assessment). Children are considered *'enrolled'* once the consent form is signed, at the start of the first in-person visit. Those who do not meet criteria for participation are considered screen failures (see ***section 5.4, Screen Failures***). For any children who are not eligible based on information gathered during the screening process, we explain the reason for their exclusion to them and thank them for their interest and time. Screening involves children completing tests and procedures to rule out concomitant impairments and to adequately describe their profile of speech, language, and cognitive skills. See ***Section 8, Study Assessments and Procedures***, for further details.

5.1 INCLUSION CRITERIA

Any child who meets all of the following criteria is eligible to participate in this study:

1. Age between 4;0 and 9;11 (years;months) at enrollment, based on parent report. To date, all studies on integral stimulation treatment methods for CAS have included children 4;0 and older. Additionally, given the summer camp setting, this age range was chosen to facilitate group activities that are age-appropriate and of interest to most children.
2. From homes where the primary language spoken is English, based on parent report. ASSIST is delivered in English and outcome measures are in English.
3. Verbal output (50+ words) and communicative intent, based on clinician and parent report. ASSIST targets speech motor planning skills to strengthen verbal communication.
4. Speech sound disorder, based on a score <16th percentile on the Diagnostic Evaluation of Articulation and Phonology (DEAP) Articulation Assessment (Dodd et al., 2006) and/or the Goldman-Fristoe Test of Articulation (Goldman & Fristoe, 2015).
5. CAS as a primary speech diagnosis, based on the following criteria:
    a. An average rating > 1 across three expert speech-language pathologists (SLPs), who will independently rate presence of CAS in children live or from video recordings of

the assessment using a 3-point scale (0 = no CAS, 1 = possible CAS, 2 = CAS). These judgments will be based on perceptual speech features of CAS (inconsistent vowel and consonant errors, difficulties achieving and transitioning into articulatory configurations, abnormal prosody), and

b. An Apraxia Score of 1 or 2 on a Maximum Performance protocol in which children sustain vowels and fricatives as long as possible and repeat syllables as fast as possible (Rvachew et al., 2005; Thoonen et al., 1999).

6. Normal hearing based on parent report or passing a standard pure-tone audiometry hearing screening at 500, 1000, 2000, and 4000 Hz (ASHA, 1997). ASSIST involves listening to and comparing self-produced and clinician-produced words and phrases, and receiving auditory verbal feedback.
7. Typical nonverbal cognition as determined by a T-score within 1.5 standard deviation (SD) of the mean on nonverbal subtests of the Reynolds Intellectual Assessment Scales (Reynolds & Kamphaus, 2003). ASSIST requires some ability to understand the cueing and feedback involved.

5.2 EXCLUSION CRITERIA

Any child who meets any of the following criteria will be excluded from participation in this study:

1. Diagnosis of disorder that significantly affects communication and/or social interactions (e.g., autism), as per referral diagnosis. These may interfere with group activities in the camp setting and with processing the visual and tactile cues that are integral to ASSIST.
2. Uncorrected vision impairments, as per parent report. These may interfere with ability to process visual cues used in ASSIST.
3. Significant impairments of oral structure (e.g., cleft palate), as judged by the SLP based on an oral mechanism exam (Robbins & Klee, 1987). These may limit speech movements for reasons unrelated to CAS.
4. A primary diagnosis of dysarthria, as judged by the SLP based on speech assessment and oral mechanism exam. Dysarthria may limit speech movements for reasons unrelated to CAS.
5. Unrelated health concerns that prevent children from participating, per parent report.
6. Inability to meet toileting needs independently or separate from parent for a full, based on parent report. Children are away from their family during the summer camp from 8 am to 3 pm and must be able to use the toilet independently.

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are placed on participating in this study. Children are allowed to continue with any regular or additional speech therapy services they receive elsewhere.

5.4 SCREEN FAILURES

Screen failures are defined as children whose family has consented to enroll them in this study but are not assigned to an experimental condition (intervention arm, e.g., Immediate vs. Delayed ASSIST, Simple vs. Complex ASSIST). For any children who are not eligible based on information gathered during the screening process, we explain the reason for their exclusion to them, and we will thank them for their interest and time. Referrals for further clinical evaluation are made as appropriate.

Children who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time (e.g., corrected visual impairment) may be rescreened. Rescreened children will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

5.5.1 RECRUITMENT STRATEGIES & NUMBER TO BE SCREENED

5.5.1.1 NUMBER TO BE SCREENED

This study does not involve a run-in period. Eligibility to participate is based on phone pre-screening and in-person screening (see ***Section 5, Study Population***, for details).

Anticipated Number to be Randomized: A priori power analysis indicates a sample size of 34 participants is needed for the primary comparison of ASSIST vs. no treatment (n=17 per group) (see ***Section 9.2, Sample Size Determination***). To account for potential attrition or smaller effect sizes than anticipated, the recruitment target is 40 (n=20 per group). Prior to screening children in person, initial eligibility and interest are determined during an initial phone or e-mail pre-screening process. Anticipated participant sample size by gender, race and ethnicity across all four studies (Cycles 1-3) is as follows:

Race	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	14	13	0	0	**27**
White	11	10	3	3	**27**
More than One Race	1	1	0	0	**2**
Total	**28**	**26**	**3**	**3**	**60**

Anticipated Number to be Screened (pre-randomization): We anticipate that there are potential participants who do not meet selection criteria either prior to consent (during pre-screening) or after consent (based on testing). Prior work in our lab showed that ~25% of children whose parents contact us do not meet initial criteria, and of those who pass pre-screening, ~20% are found ineligible during screening. Based on these estimates, we anticipate initial contact with parents of ~100 children to

screen 75 children and achieve a sample of 60 children who are eligible and randomized. Anticipated contact across all four studies (Cycles 1-3) is as follows:

Race	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	4	4	0	0	**8**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	23	21	0	0	**44**
White	18	16	5	5	**44**
More than One Race	2	2	0	0	**4**
Total	**47**	**43**	**5**	**5**	**100**

5.5.1.2 PLANNED RECRUITMENT STRATEGIES

Recruitment involves sharing study advertisements in multiple ways and with multiple audiences and through word of mouth: (1) referrals from the local community, (2) existing databases of children/parents who have indicated permission to be contacted about research opportunities, (3) responses to recruitment materials in the community and at community outreach/education events, and (4) advertisements in newsletters and announcements on websites.

(1) Referrals from the local community. We contact teachers and clinicians in local schools (e.g., School District of Philadelphia), and physicians, speech-language pathologists, or other clinicians in the community. This includes local hospitals (e.g., Children's Hospital of Philadelphia), local Intermediate Units (educational service agencies who interface with Pennsylvania schools), and private practitioners. Contingent upon appropriate approvals, referral sources either distribute recruitment materials to parents/legal guardians of potential participants, who then contact the research team directly, or referral sources provide contact information of parents/legal guardians of potential participants to the research team (with parent/legal guardian's permission), who then contact the parent/legal guardian directly. The Temple University Department of Communication Sciences and Disorders alumni e-mail list is used (with appropriate permission from alumni list manager) to reach out to SLPs in the community.

(2) Existing databases. We use existing databases to contact participants who have previously participated in departmental studies or clinical services and whose parents/legal guardians have agreed to be contacted for research. This includes the lab's own research database of participants who have in the past participated or expressed interest in research studies, as well as the CSD Speech-Language-Hearing Center at Temple University, and databases from other researchers in the CSD department. The persons in charge of or responsible for the database either distribute recruitment materials to these individuals or provide the research team with the contact information, after which the research team contacts the parents/legal guardians of the potential research participants.

(3) Community outreach events. We distribute recruitment materials to speech and language clinics and organizations in the community (e.g., YMCA) and at community outreach and educational events attended by parents and/or SLPs (e.g., in-services, Philadelphia Apraxia Walk).

(4) Advertisements: Advertisements are placed in newsletters or on websites such as Philly Parent Circle and the Childhood Apraxia of Speech Association of North America (contingent on appropriate approvals) that are likely to reach our target population and foster a demographically representative sample. Advertisements contain contact information, and parents/legal guardians of potential research participants contact the research team directly. Our lab website also has a sign-up form for parents who seek treatment research opportunities.

5.5.2 RETENTION STRATEGIES

Given the near-daily contact during camp weeks, visit reminders are generally unnecessary but are sent if requested or necessary. For assessment visits, parents receive e-mail or phone reminders within a few days of the appointment.

The following strategies are implemented to retain children for the duration of each study:

(1) We explain the importance of completing the study to the parents before enrolling so that they can make a decision whether they wish to enroll their child. If a parent decides to withdraw their child after enrollment, we will ask if they are nevertheless willing to return for post-testing to minimize data loss.

(2) We offer the treatment at no cost to parents (nor is insurance involved). This provides an incentive for all parents, and reduces the risk of differential attrition by socio-economic status.

(3) We offer the treatment in a relatively short period of time (7 weeks in summer, plus evaluation prior to treatment). This reduces the risk of life events impacting attrition (e.g., moving away).

(4) We offer the treatment as a Summer Camp experience, where parents drop off their children in the morning and pick them up in the afternoon at fixed times. This facilitates scheduling and forming a routine, and allows parents to conduct their normal affairs during the day. We provide snacks for the children but ask parents to pack a lunch for their children.

(5) We strive to make the Summer Camp fun for the children. Each day has a variety of group activities, conducted by trained camp counselors (supervised by a camp leader) who have experience working with children. Children may do arts and crafts and take their projects home. Children may also earn small prizes as rewards during their treatment sessions.

(6) We offer to share copies of evaluation reports with the parents, as well as copies of treatment progress and resulting publications (after completion of the study).

5.5.3 PARTICIPANT INCENTIVES

There are no monetary incentives for participants. The intervention and summer camp experience are offered at no cost to families. Children may earn small prizes as rewards during their treatment sessions. Children may create arts and crafts and may take their creations home.

5.5.4 VULNERABLE POPULATIONS

This research includes individuals who are not yet adults. In particular, this research recruits and enrolls children between the ages of 4;0 (years;months) and 9;11 who have been diagnosed with CAS, because the purpose of the research is to gain information about the initial efficacy and optimal parameters of a treatment for CAS. Children younger than 4;0 are excluded due to the attentional demands required for the proposed treatment. To date, all studies on integral stimulation treatment methods for CAS have included children 4;0 and older. The age range is limited because, as an initial Phase 1 study, the goal is to include a relatively narrow population to detect an initial effect in the intended population. Further, given the summer camp setting, a limited age range facilitates planning group activities that are likely age-appropriate and of interest to the children.

Recruitment strategies and risk management strategies are described above in ***Section 5.5., Strategies for Recruitment and Retention***, and ***Section 2.3, Risk/Benefit Assessment***.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION AND EXPERIMENTAL MANIPULATIONS ADMINISTRATION

ASSIST is an intervention for children with CAS that targets speech motor planning skills by practicing personally relevant words or phrases with cueing support and verbal feedback. Practice is systematically adaptive based on in-session performance to maintain practice at the child's optimal challenge level and structured in accordance with principles of motor learning.

ASSIST is designed for children with a range of CAS severities and is informed by prior CAS treatment literature (Edeal & Gildersleeve-Neumann, 2011; Maas et al., 2012, 2014, 2019; Maas & Farinella, 2012; Strand & Debertine, 2000; Strand et al. 2006), clinical insights, and the motor learning literature (Maas et al., 2008; Schmidt, 1975, 2003; Schmidt et al., 2018). The proximal target is improved speech motor planning skills (through specific practice; see ***Section 6.1.2, Administration and/or Dosing*** for details) as measured by perceptual speech accuracy, because impaired speech accuracy is presumed to be the main cause of reduced intelligibility and participation (more distal outcomes). However, it is important to note that ASSIST itself does not target ICF domains beyond Body Functions; rather, it is conceived as part of a broader pathway towards distal goals.

6.1.1 ADMINISTRATION AND/OR DOSING

6.1.1.1 COMMON PROCEDURES

6.1.1.1.1 DOSAGE

The intervention (16 hours of ASSIST) is delivered over 2 weeks, with four 30-minute sessions per day (4 days/week), except for the Distributed ASSIST group in Study 4, who receive the intervention over 4 weeks, with two 30-minute sessions per day (4 days/week). In all cases (for each child) there is at least 1 hour between individual ASSIST sessions.

6.1.1.1.2 INTERVENTIONISTS

In each recruitment cycle (summer), ASSIST is delivered by 5 graduate student clinicians ("SLPs") supervised by experienced and licensed SLPs with expertise in CAS ("supervisors"). The SLPs are students in Temple University's Speech-Language Pathology clinical Master's program and complete this intervention experience as part of a clinical externship towards their Master's degree. All SLPs have completed a graduate course on pediatric speech sound disorders and a clinical rotation in the university clinic with CAS clients prior to participating as interventionists in this trial. They receive extensive training on the ASSIST intervention and study protocol.

Each clinician is assigned 4 children as clients, two per phase (Immediate, Delayed) and condition (Simple/Complex, Word/Nonword, Massed/Distributed). Assignment of children to clinicians is based on clinical judgment and avoidance of prior relationship between clinician and child.

6.1.1.1.3 ASSIST PROCEDURES

ASSIST, an integral stimulation-based CAS treatment based on clinical insights and principles of motor learning (Maas et al., 2008; Schmidt et al., 2018) and neuroplasticity (Kleim & Jones, 2008; Ludlow et al., 2008) (***Table 1***), targets speech accuracy with systematic, adaptive practice on meaningful targets (words and phrases). ASSIST shares features with other motor-based CAS treatments but differs in its specific operationalization of target selection (the "what") and systematic adaptive practice (the "how").

Table 1. Principles of neuroplasticity and motor learning in ASSIST. FB = feedback; KR = knowledge of results; KP = of performance.

Principle	Pre-Practice	Practice
Salience	Functionally relevant targets	
Amount	16 hrs of ASSIST; 4 utterances/session	
Attention	Focus on sound & movement	
Variability	Targets embedded in 3 different frames	
	Constant prosody	Variable prosody
Schedule	Blocked	Random
Main FB type	KP	KR
FB timing	Immediate	Delayed (2-3 sec.)
FB frequency	100%	Reduced (fading)

The "What" of ASSIST. Children practice *targets* embedded in different *frames*. Targets: Each child has a set of 30 words/phrases that are *personally meaningful* (to boost motivation and carryover potential) and *within the child's optimal challenge range*[241] (to boost motivation and expectancies through success and increase task attention by minimizing frustration) based on phonetic inventory and baseline accuracy. For Study 3 (Lexicality), we also create 30 corresponding *nonwords* by changing a stressed

vowel (and 0+ other sounds), maintaining stress and complexity (e.g., *banana – banoono)*. In any session, children practice only 4 targets to maximize practice amount for those targets. Frames: Targets are embedded in 3 *frames* (target + frame = *utterance*) to bolster communicative relevance, practice variability, sequencing/prosodic skills, and engage language to boost a weak link between language and speech motor planning (Shriberg et al., 2012). Frames are real words (*hi mom*) or sounds (*mommy*), designed to be functional and achievable, and differ in complexity (Jakielski, 2016) to create systematic step-up/down options.

The "How" of ASSIST . ASSIST is designed to facilitate both in-session performance and learning (Kantak & Winstein, 2012; Lai et al., 2000; McIlwaine et al., 2010; Maas et al., 2008; Rosenbek et al., 1974; Schmidt et al., 2018). Sessions are divided into *Pre-Practice* and *Practice*. Mastered utterances move to *Maintenance*.

Pre-Practice: Pre-Practice prepares the child to take advantage of Practice by ensuring motivation and showing that the utterance is within reach (with maximal cueing if needed). Pre-Practice is designed to facilitate in-session improvement and establish motor patterns. The SLP elicits utterances via integral stimulation in blocks of up to 5 attempts, providing immediate feedback and cues needed; blocks are randomized. Once an utterance is produced correctly, it will not be elicited further; Pre-Practice ends after 1 accurate response for each utterance or 15 minutes.

Practice: Practice provides as many opportunities as possible to gain experience with assembling and producing utterance motor plans. In 4-minute *Practice Runs* children engage in intensive structured speech motor practice supported by SLP cues and feedback in 'test-teach-retest' sequences called *Teaching Episodes* (TE). In 'test' and 'retest' phases, the SLP elicits utterances and provides KR feedback; during the 'teach' phase, the SLP can provide KP feedback and support (e.g., tactile cues; slow rate) to elicit 2 additional attempts. Practice is systematically adapted to the child's in-session performance, by varying (a) elicitation method (immediate and delayed imitation, independent production), (b) frame and (c) target, based on operationalized step-up/step-down criteria. Utterances mastered in independent production are moved to Maintenance. When all frames for a target are mastered, a new target is introduced.

Maintenance. Mastered utterances are elicited in Independent Production twice (in random order) at the start of each second session; if accuracy drops to 0%, the utterance is moved back to Practice.

6.1.1.1.4 SETTING

Context. The study takes place in the context of a 4-week summer day camp at Temple University's main campus in Philadelphia, in the Department's Speech-Language-Hearing Center (university clinic) and the PI's Speech, Language, and Brain Laboratory (SLAB Lab). The space consists of six small clinic rooms with child-appropriate furniture for individual ASSIST pull-out sessions; two large rooms for group activities; a large meeting room for daily clinician meetings; and a gated outdoor green space for outdoor activities.

During camp weeks, children attend camp four days per week (Monday, Tuesday, Thursday, Friday) from 8:00 am to 3:00 pm. Families drop off and pick up their children but do not enter the building or observe during the day. For indoor activities, children are divided into groups roughly by age and personality

based on clinical judgment. Drinks and snacks are provided, but families provide lunch and other necessities (e.g., sun block, extra clothes) for their children. ASSIST is delivered in a "pull-out" model where children leave the group room for individual ASSIST sessions throughout the day.

Purpose. The purpose of offering ASSIST in a summer camp format is threefold. First, offering treatment during the summer reduces the number of children who receive speech therapy elsewhere (e.g., in school). Second, a camp format facilitates attendance for the intensive treatment schedule, with two hours per day, divided over four sessions throughout the day. A free-of-charge day camp is expected to increase the representativeness of the sample by minimizing economic barriers to participation (e.g., cost, transportation). Third, a camp format creates a relatively comparable daily environment for children receiving treatment and those not (yet) receiving treatment. Finally, although not a design-related consideration, a camp format also provides a positive and fun environment for the children.

Philosophy. The philosophy of the camp is to focus on fun, respect, inclusion and acceptance, and naturalistic communication in whatever mode is preferred by the child. There is no focus on speech practice, and camp staff does not know a child's targets or treatment condition, because the camp environment constitutes the untreated control condition. Group activities include gross-motor games, story time, arts and crafts. Children are not required to participate in group activities and are allowed to play by themselves or read a book. Any group activities and games are designed or adapted to ensure all children are able to participate, and games with clear competition and winners and losers are avoided in favor of more collaborative games and activities.

Camp Staff. Camp staff includes 2 camp leaders and 12 camp counselors, for an Adult:Child ratio of approximately 1.5:1. Each group room has a camp leader and 6 camp counselors. Each child is assigned one camp counselor as primary 'buddy' to establish rapport and ensure each child's well-being, and to timely drop off and pick up the child from individual treatment sessions. Each camp counselor has no more than two children assigned as their buddies. Camp counselors are responsible for looking after the child's needs and making sure children arrived at their 30-minute sessions ready and on time.

Camp staff are trained on how to communicate with children with CAS, including via small communication boards worn by all staff and children, children's own alternative and augmentative communication devices, gestures, or speech. Camp staff also receive detailed training on camp tasks and logistics, division of labor, emergency procedures and policies and expectations. They are familiarized prior to camp with the enrolled children's profiles, background, likes, and dislikes to facilitate communication, planning, and rapport-building.

6.1.1.2 STUDY-SPECIFIC MANIPULATIONS

6.1.1.2.1 STUDY 1 (ASSIST VS. NO ASSIST)

Study 1 compares ASSIST to No-ASSIST. Procedures, dosage and target selection are as above (see ***Section 6.1.2.1.3, ASSIST Procedures****, The "How" of ASSIST*).

6.1.1.2.2 STUDY 2 (SIMPLE ASSIST VS. COMPLEX ASSIST)

Study 2 compares Simple vs. Complex ASSIST. Procedures, dosage, and target selection are as above. The experimental manipulation for complexity involves *frame* complexity: In Simple ASSIST, Index of Phonetic Complexity (IPC) of frames range from 0 to 2, whereas in Complex ASSIST, frame IPC values range from 3 to 5.

6.1.1.2.3 STUDY 3 (WORD ASSIST VS. NONWORD ASSIST)

Study 3 compares Word vs. Nonword ASSIST. Procedures and dosage are as above. The experimental manipulation for lexicality involves whether targets are words or nonwords. Target selection is the same as above except that for each individual word target, a nonword counterpart is created by changing one stressed vowel and 0 or more other sounds in the real words. Thus, all participants have 60 items (30 words, 30 nonwords), and are allocated randomly to receive ASSIST either for real word targets or for nonword targets. Nonwords are embedded in real-word frames (same as the words) and are paired with made-up creatures as referents for elicitation and pragmatics.

6.1.1.2.4 STUDY 4 (MASSED ASSIST VS. DISTRIBUTED ASSIST)

Study 4 compares Massed vs. Distributed ASSIST. Procedures and target selection are as above. Dosage is as above for the Massed ASSIST group. For the Distributed ASSIST group, intervention is delivered 1 hour per day (two 30-minute sessions), 4 days per week for 4 weeks (16 total hours of ASSIST).

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Treatment fidelity is facilitated by: (a) a manualized protocol, (b) extensive training including video review and role play on the ASSIST protocol, (c) “hard-coding” decisions on tracking sheets, and (d) direct observation and joint (team) decision-making at daily debriefs. (e) Independent analysts review randomly selected treatment sessions for adherence to protocol. Each SLP provides intervention in both conditions per study to control for possible provider confounds on condition effects.

(a) A manualized protocol (Clinician Manual) specifies the rationale, principles, targets, and techniques and procedures of ASSIST.

(b) Training involves approximately 15 hours of group-based in-person introduction and understanding of ASSIST, including CAS and treatment rationale and structure. Procedures are illustrated with video examples, and all aspects of ASSIST are practiced to familiarity through role plays (e.g., multimodal cueing, providing different types of feedback, pre-practice procedures, practice procedures, stepping up and down based on performance).

(c) In-session decisions are "hard-coded" on session tracking sheets. These decisions include randomized order of presentation, whether to step up or down an elicitation level, provide feedback, and elicit additional attempts, and when to take a break. The tracking sheet also contains The tracking sheet also informs between-session decisions about changing targets and frames.

(d) Supervisors observe sessions in real time and can intervene and provide feedback regarding protocol fidelity. In addition, end-of-day debriefs during camp will include review of fidelity concerns for immediate correction and consistency across SLPs.

(e) Independent analysts review randomly selected treatment sessions from each child for adherence to the intervention protocol, based on video review. Factors considered are those related to critical ingredients and intervention dosage.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

True blinding of SLPs and children is impossible. We adopt multiple strategies to minimize bias and ensure validity of the data.

(1) The study and intervention are conducted during the summer, to minimize effects of history, in particular concurrent intervention received elsewhere. The intensity of the summer camp (4 days/week for 4 weeks) reduces likelihood that children receive concurrent external speech therapy.

(2) We use randomization to assign children to conditions to eliminate confounds in child-related factors (e.g., severity, age) with equal probability in each study. Randomization is determined by the biostatistician (Co-I Wu) who will not interact with children, parents, or SLPs. Allocation is concealed in consecutively numbered opaque envelopes until after eligibility is confirmed. Reveal of allocation for all children in a recruitment cycle occurs only after recruitment is complete and the final sample of eligible children is known. Allocation is revealed for all children in a lab meeting with at least three team members present to avoid error. (See ***Section 4.1, Overall Design***).

(3) We use blinded data collectors to obtain speech samples for outcome measures. To maintain blinding, data collectors will not be present at the summer camp during treatment blocks and thus will not see which children are pulled out. The same data collectors will collect data from all children in a study and will collect data at all three timepoints. Importantly, a data collector will never test the same child more than once, to avoid possible effects of familiarity and bias in elicitation (stimuli are pre-recorded to ensure consistency of elicitation model). There is no planned unblinding of data collectors. Inadvertent unblinding is logged.

(4) We use blinded data assessors. Speech accuracy will be scored by research assistants who were not involved in summer camp or probe data collection. Clues regarding treatment status or time point (e.g., reference to upcoming holidays) will be removed from audio recordings and file names by a research assistant not involved in data analysis. Inter-rater reliability will be assessed for 10% of data using Krippendorff's alpha. There is no planned unblinding of data assessors. Inadvertent unblinding is logged.

(5) We use blinded statistical analysis. Dr. Wu (biostatistician) does not know group (Immediate or Delayed) or condition status (Simple/Complex, Word/Nonword, Massed/Distributed) and does not interact with the children or families. There is no planned unblinding of the statistician until after completion of final analysis. Inadvertent unblinding is logged.

(6) We use blinded camp staff. Camp staff is blinded to a child's condition and targets (blinding to phase is not possible as camp staff is responsible for bringing children to and from their individual sessions). There is no planned unblinding of camp staff. Inadvertent unblinding is logged.

(7) We adopt equipoise in all communication about the study, including in lab meetings, training of research personnel (including treating SLPs), and interactions with children and parents. For each study, we present both conditions as potentially beneficial, never referring to any condition as "no treatment" or "optimal treatment". They will simply be referred to by their condition (e.g., Simple vs. Complex, Individual vs. Group activities). This will minimize potential bias on the part of SLPs, children, and parents (who complete ratings of intelligibility and communicative participation).

(8) Parents are not informed of their child's assigned phase (Immediate or Delayed), condition (Simple/Complex, Word/Nonword, Massed/Distributed), or targets, to minimize placebo effects on caregiver-reported outcome measures. Parents do not observe treatment sessions and are thus not aware of which items are being treated. Parents may discover this information from their children. Follow final data collection (T3), families report whether they knew their child's phase and condition, and are informed of the actual allocation. Inadvertent unblinding is logged.

(9) We use the same clinicians across conditions in each recruitment cycle to control for clinician confounds. Each clinician will treat an equal number of children in each condition.

(10) Treatment fidelity will be facilitated by a manualized protocol, extensive training including video review and role play, "hard-coding" in-session decision on session tracking sheets, and real-time observation and daily team debrief discussions (see ***Section 6.2, Fidelity***). Independent research assistants also review randomly selected videos of treatment sessions for adherence to protocol.

(11) We create target sets before randomization to avoid bias.

(12) We use pre-recorded auditory models to elicit primary outcome data samples (imitation of individualized target words and phrases). This controls for any differences between or within data collectors in terms of dialect or speaking style, which may affect how a child says a target.

(13) Outcome data collection occurs in a different room from the room where a child received treatment in order to avoid possible inflation of effects due to contextual cue effects.

(14) Diagnosis of CAS is rigorous in that it is based on *both* a rigorous clinical SLP expert criterion (see 15 below) *and* the Maximum Performance Task protocol (Thoonen et al. 1996, 1999), the only prospectively validated tool with strong diagnostic accuracy for CAS.

(15) We use an operationalized criterion of CAS clinical diagnosis based on clinical expert judgment from three independent recognized expert SLPs (CAS3SLP score > 1).

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The Summer Camp setting is designed to maximize attendance for intervention sessions. Attendance is facilitated by stating the fixed dates of the study in advance (including on recruitment materials), by providing a detailed week-by-week camp schedule before the start of camp, and by daily contact with families during drop-off and pick-up. Absences will be logged daily during camp weeks to enable adjustment for amount of intervention received.

During intervention sessions, adherence to protocol may be reduced due to frustration experienced by the child during difficult treatment tasks. SLPs provide a supportive environment, clear structure with visual supports, and breaks with engaging fun activities to manage the child's behavior and motivation to continue to engage Tracking sheets are completed each session to log the number of teaching episodes completed, and which targets and utterances are practiced how many times. All sessions are audio- and video-recorded for off-line review. Parents must agree to have their child recorded for data analysis and verification purposes in order to participate (additional uses of recordings are optional).

6.5 CONCOMITANT THERAPY

No restrictions are placed on participating in this study. Children are allowed to continue with any regular or additional speech therapy services they receive elsewhere (usual care). We ask parents to disclosure any concomitant speech therapy prior to the start of camp as well as after T3 data collection. Any details about concomitant therapy (received, amount, type) is documented in the participant data file. Concomitant speech therapy is unlikely given the intensity and full-day commitment (8:00 am – 3:00 pm, 4 days/week for 4 weeks).

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

We do not anticipate serious adverse events from the intervention. However, we monitor child frustration during treatment sessions throughout the trial, as described below.

Treating speech-language pathology (SLP) graduate students note in daily treatment progress notes the degree of each child's frustration level on a 4-point scale involving the SLP's judgment based on behavior observed during the session (e.g., crying, refusal to speak). In this scale, 0 = no frustration, full

compliance with procedures throughout session; 1 = some frustration, occasional non-compliance with procedures during session; 2 = significant frustration, frequent non-compliance with procedures during session; 3 = marked frustration, non-compliance during entire session).

SLPs discuss with the PI, Co-I Caspari, and the SLP supervisors at the end of each treatment day those children who are judged to experience significant or marked frustration (scores of 2 and 3) in a session. On a daily basis during Summer Camp, this team discusses possible strategies to minimize or eliminate the child's frustration in subsequent sessions. For children who experience recurrent significant or marked frustration (scores of 2 or 3 across more than three consecutive treatment days), the PI and Co-I Caspari will discuss with parents the options of continuing or withdrawing from the study. The PI is responsible for reporting withdrawals to the IRB.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

7.2.1 INDIVIDUAL PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants are free to withdraw from the study at any time and for any reason without consequence by contacting the Investigator or appropriate research personnel. Data to be collected on discontinuation of ASSIST will include the reason(s) for discontinuation. When a child discontinues from the ASSIST intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol. Withdrawal from this study does not preclude children from participating in future studies in the SLAB Lab or any other lab at Temple University, nor does it jeopardize any other relationship with Temple University they may have now or in the future (including clinical services through the TU Speech-Language-Hearing Center). Parents and children are informed during the consent process of their right to withdraw at any time.

We do not anticipate withdrawing participants without their consent. However, participants may be withdrawn from the study:

- If they develop a medical condition that makes it difficult to continue or may be contagious.
- If they meet an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- If they repeatedly fail to follow study procedures or experimenter directions which would make it impossible to obtain usable data (e.g., repeatedly refusing to follow the clinician's directions).
- If they repeatedly fail to show up for scheduled appointments. Repeated cancellations may result in data that is incomplete or difficult to interpret. Such situations would be wasteful of valuable resources, and participants may be withdrawn from the study without their consent. If this occurs, the PI or appropriate research personnel will make a reasonable attempt to explain the reason for withdrawal. We expect that participants will attend their scheduled appointments and will contact us if they need to reschedule.

The reason for participant discontinuation or withdrawal from the study will be recorded on the ASSIST Case Report Form (CRF). Children who are randomized will not be replaced regardless of whether they have received any intervention.

7.2.2 COHORT DISCONTINUATION/WITHDRAWAL: TRIAL STOPPING RULES

Study procedures, including intervention, may be discontinued for all participants under the following circumstances:

Adverse events: In this minimal risk study, we do not anticipate any significant adverse events. However, if 10 or more children in Cycle 1 or 2 experience recurrent significant or marked frustration (as described above in ***Section 7.1, Discontinuation of Study Intervention/Experimental Manipulation***), subsequent cycles will not be initiated regardless of whether children withdraw (e.g., if 10 or more children with significant or marked frustration in Cycle 1, then Cycle 2 will not be initiated).

Attrition: Although unlikely, it is possible that children will withdraw from the study, either because of recurrent frustration with study procedures or for other reasons. Based on our prior research and clinical experience with similar intensive summer camps, we do not anticipate many, if any, withdrawals. Estimates of statistical power with reduced sample sizes reveal that with attrition rates below 25% (drop-out of fewer than 5/20 children per year), we still have adequate power to detect anticipated effects. In the highly unlikely event that withdrawals exceed 5 children in any year, the research team (PI, Co-I Caspari, Co-I Wu) and the Key Consultants (Gildersleeve-Neumann & Stoeckel) will discuss what, if any, action should be taken to improve retention and whether to discontinue the study. Because this study represents the first RCT of integral stimulation treatment for CAS with the largest sample size to date, it might still be of interest to continue the study to provide critical information for design, development, and implementation of future clinical trials by our team and others.

Lack of efficacy: Given that this study represents a Phase 1 initial efficacy study for a novel treatment with a no-treatment comparator, no efficacy guidelines are available to determine a stopping criterion based on lack of efficacy. In addition, data analysis (blinded speech accuracy judgments and intelligibility) will only be completed after conclusion of each summer camp. As such, stopping each study for lack of efficacy before concluding the summer camp is not possible. However, analysis of Study 1 will inform optimal treatment targets for Study 2, and analysis of Study 2 will inform targets for Study 3, in order to minimize the potential risk of lack of efficacy (e.g., if complex targets lead to larger gains in Study 1 with real word targets, then Study 2 will compare complex words with complex nonwords).

7.3 LOST TO FOLLOW-UP

A child will be considered lost to follow-up if he or she fails to return for T2 or T3 data collection visits and study staff are unable to contact the family after at least 3 attempts (phone and e-mail). Attempts at contact will be documented in the participant file.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Children with CAS complete screening procedures, intervention procedures, and data collection procedures. See ***Section 6.1, Study Intervention and Experimental Manipulations Administration*** and Clinician Manual for description of intervention procedures. Intervention is administered by SLP graduate students under supervision of a certified, licensed, and experienced SLP.

8.1.1 SCREENING

Children complete tests and procedures to rule out concomitant impairments and to adequately describe their profile of speech, language, and cognitive skills. Responses are recorded on score forms, and any task that requires the child to produce a verbal response is audio and/or video recorded for data analysis and reliability assessment. These tests and procedures are administered within 3 months prior to camp start by SLP graduate students supervised by certified, licensed, and experienced SLPs.

Screening includes the following:

(1) Pure-Tone Hearing Screening at 0.5, 1, 2, and 4 kHz (ASHA, 1997), to ensure adequate hearing. This involves wearing headphones and responding to tones by raising a hand.

(2) Dynamic Evaluation of Motor Speech Skill (DEMSS; Strand & McCauley, 2019), a dynamic assessment protocol in which a child's ability to produce certain sounds and sound sequences consistently correctly is assessed with different levels of support (e.g., with visual or tactile cues).

(3) Diagnostic Evaluation of Articulation and Phonology (DEAP; Dodd et al., 2006) and/or Goldman-Fristoe Test of Articulation (GFTA; Goldman & Fristoe, 2015), to determine presence & severity of speech disorder. These tests involve naming pictures of familiar items and retelling a story or repeating sentences; they sample English consonants in all word positions.

(4) Oral Mechanism Examination (OME; Robbins & Klee, 1987), to evaluate oral structure and function. This involves tasks such as opening the mouth and sticking out the tongue, or blowing bubbles through a straw.

(5) Maximum Performance Tasks (Thoonen et al., 1999), to evaluate speech motor capabilities and identify specific types of motor speech disorders in children. This test includes tasks such as saying 'ah' or 'sss' as long possible, or repeatedly saying 'pataka' as fast as possible.

(6) Clinical Evaluation of Language Fundamentals (CELF; Semel et al., 2004), to evaluate language skills. This test includes tasks such as finishing sentences after the examiner, repeating sentences, and pointing to pictures in response to examiner's prompts.

(7) Peabody Picture Vocabulary Test (PPVT; Dunn & Dunn, 2007), to evaluate receptive vocabulary. This test asks children to point to a color picture (out of an array of four pictures) that matches the examiner's spoken word.

(8) Expressive Vocabulary Test (EVT; Williams, 2007), to evaluate expressive vocabulary. This test asks children to provide one-word responses to a question about a color picture (e.g., What do you call this animal? "A dog").

(9) The Phonological Awareness subtests of the Comprehensive Test of Phonological Processing (CTOPP; Wagner et al., 1999), to evaluate phonological awareness skills. This test involves tasks such as identifying which two of three pictures (with spoken word) start or end with the same sound.

(10) The nonverbal subtests of the Reynolds Intellectual Assessment Scales (RIAS; Reynolds & Kamphaus, 2003), to evaluate nonverbal cognitive skills. This test involves tasks such as identifying the 'odd-item-out' in a picture array, without requiring a verbal response.

(11) The Diagnostic Evaluation of Articulation and Phonology (Dodd, Hua, Crosbie, Holm, & Ozanne, 2006) to evaluate consistency of speech errors. This test asks children to name a set of pictures several times, in random order, so that consistency of errors can be evaluated.

(12) A single-word naming task involving 50 multisyllabic words to evaluate syllable sequencing and lexical stress. In this non-standardized test, children name pictures or repeat multisyllabic words (e.g., elephant, helicopter). A similar test has been used previously with children as young as 4 years 0 months (Gozzard et al., 2008).

(13) The Syllable Repetition Task (SRT; Shriberg et al., 2012; Shriberg & Lohmeier, 2008) to evaluate children's ability to repeat progressively longer sequences of simple syllables. This task is implemented on a computer in PowerPoint, with pre-recorded models. The items include the following: bada, dama, bama, mada, naba, daba, nada, maba, bamana, dabama, madaba, nabada, banada, manaba, bamadana, danabama, manabada, nadamaba.

(14) A connected speech sample will also be collected to characterize the nature and consistency of speech errors and prosody. Connected speech samples may involve free conversation and/or based on picture description (for example the Park Play scene; Patel & Connaghan, 2014).

Parents also complete the following:

- Contact information form (address, preferred contact method, and emergency contact).
- Background questionnaire about developmental milestones, language background, and other information relevant to understanding the child's speech and language profile and context. This questionnaire is administered at the first visit during the pre-camp period.
- Functional communication questionnaire (Wilson & Gildersleeve-Neumann, 2014) to solicit a list of potential treatment targets based on personal interests and needs. Together with parent and child, the research team reviews for completeness and clarity and to prioritize possible targets for inclusion in treatment. This questionnaire is administered during the pre-camp period.

Finally, with parents' permission, we also seek further information from existing records elsewhere, which may include speech-language pathology evaluation reports and treatment notes, neurological reports and scans, neuropsychological test results, and Individualized Educational Programs. This information provides further background information that will facilitate interpretation of the findings.

Screening takes place within 3 months of camp start within a recruitment cycle, and involves up to 7 hours of testing divided over 2-7 sessions depending on child stamina and scheduling availability. For diagnosis of CAS, three expert SLPs (Co-I Caspari and the two Key Consultants Dr. Gildersleeve-Neumann and Dr. Stoeckel) each provide an independent rating based on live or video-recorded sessions. Video recordings are shared with Key Consultants via TU SafeSend, a secure file sharing system hosted by Temple University. Rating for presence of CAS uses the CAS3SLP scale, which includes 3 options: 0 = no CAS, 1 = possible CAS, 2 = CAS. To meet inclusion criterion 5a (clinical judgment of presence of CAS; see ***Section 5.1, Inclusion Criteria***), children must receive a mean CAS3SLP score (across the three expert SLPs) > 1. Expert SLPs share their rating with the PI, who aggregates the ratings to determine eligibility.

8.1.2 DATA COLLECTION & STUDY ENDPOINTS

Data is collected by trained Data Collectors blinded to a child's treatment status, condition, and targets.

Primary efficacy outcome endpoint:

- Perceptual accuracy of treated items, judged by blinded research assistants from audio recordings. Children repeat a list of words and nonwords after a pre-recorded model (played over speakers). These speech samples serve as the basis for the primary outcome measure. Three Data Analysts (different from Data Collectors) use the three-way perceptual scoring system (e.g., Maas et al., 2012; Strand et al., 2006) to score accuracy of children's productions. Data Analysts are blinded to a child's treatment status, condition, and targets. The three-way scoring system assigns 2 points for completely correct responses, 1 point for responses with one minor error (operationally defined), and 0 points for a major error (operationally defined) or multiple errors. Scoring reliability is assessed using intra-class correlations (ICC) (single-rater two-way random effects model for absolute agreement; Hallgren, 2012; Koo & Li, 2016). Mean across analysts will be used in analysis.

Secondary efficacy outcome endpoints:

- (SE-1) Perceptual accuracy of the full 30-item set of potential targets, judged by blinded data analysts from audio recordings. Children repeat a list of words and nonwords after a prerecorded model (played over speakers). These speech samples serve as the basis for this outcome measure. Three Data Analysts (different from Data Collectors) use the three-way perceptual scoring system (e.g., Maas et al., 2012; Strand et al., 2006) to score accuracy of children's productions. Data Analysts are blinded to a child's treatment status, condition, and targets. The three-way scoring system assigns 2 points for completely correct responses, 1 point for responses with one minor error (operationally defined), and 0 points for a major error or multiple errors. Scoring reliability is assessed using intra-class correlations (ICC) (single-rater two-way random effects model for absolute agreement; Hallgren, 2012; Koo & Li, 2016). Mean across analysts will be used in analysis.

- (SE-2) ICS: Parent rating of their child's intelligibility in context, using the Intelligibility in Context Scale (ICS; McLeod et al., 2012, 2015). The ICS is completed by the same parent at each time point to control for differences between parents' perspectives.
- (SE-3) FOCUS-34: Parent rating of their child's communicative participation, using the Focus on Outcomes of Communication Under Six (FOCUS-34; Thomas-Stonell et al., 2012). The FOCUS-34 is completed by the same parent at each time point to control for differences between parents' perspectives.
- (SE-4) TOCS+ Intelligibility: Percentage of words correctly understood from the audio recording by blinded unfamiliar listeners. Speech samples are obtained using the computerized Test of Children's Speech (TOCS+) Intelligibility test (Hodge et al., 2009, 2012, 2014a,b). The TOCS+ Intelligibility test is a computerized instrument that selects words or sentences from an item bank (individualized to the child's language abilities). Children repeat words and sentences. The word portion of the TOCS+ selects 78 words from a larger set, and the sentence portion creates a list of sentences selected from over 2,000 unique sentences (each sentence portion contains no more than 80 words, divided over a variable number of sentences depending on sentence length). Children repeat these items and listeners transcribe the child's utterances.

8.2 SAFETY ASSESSMENTS

Primary safety endpoint:

- Child frustration during intervention sessions (scores of 2 or 3 across more than 3 consecutive intervention days).

Child frustration levels are rated by the treating SLP at the end of each session on a 4-point scale where 0 = no frustration, full compliance with procedures throughout session; 1 = some frustration, occasional noncompliance with procedures during session; 2 = significant frustration, frequent non-compliance with procedures during session; 3 = marked frustration, non-compliance during entire session.

Treating SLPs monitor child frustration and, immediately after each intervention session, rate the degree of each child's frustration level on a 4-point scale based on the treating SLP's clinical judgment of behavior observed during the session (e.g., crying, refusal to speak). In this scale, 0 = no frustration, full compliance with procedures throughout session; 1 = some frustration, occasional non-compliance with procedures during session; 2 = significant frustration, frequent non-compliance with procedures during session; 3 = marked frustration, non-compliance during entire session.

Scores of 2 and 3 prompt review and discussion by the PI, Co-I Caspari, and the clinical team (treating SLPs and SLP supervisors) to identify strategies to minimize frustration. For children who experience repeated significant or marked frustration (average daily scores ≥ 2 across more than three consecutive intervention days), the PI and Co-I Caspari will discuss with parents the options of continuing or withdrawing from the study. Safety review by the PI and Co-I Caspari occurs daily clinical team debrief meetings at the end of each intervention day.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the following definition of adverse event (based on Inspector General guidance for HHS regulations 45 CFR part 46: Any untoward or unfavorable occurrence in a human participant, including any abnormal sign or symptom temporally associated with the child's participation in the research, whether or not considered related to the child's participation in the research.

In this minimal risk trial, no physical or medical adverse events are anticipated. Potential adverse outcomes that are recorded are psychological, in particular child frustration during intervention sessions (scores of 2 or 3 across consecutive intervention days).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events are defined as significant negative effects on health or safety (including physical injury or death) caused by, or associated with, an intervention.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines are used to describe severity.

- **Mild** – Consistent frustration ratings of 2 across more than three consecutive intervention days.
- **Moderate** – Consistent frustration ratings of 2 and 3 across more than three consecutive intervention days.
- **Severe** – Consistent frustration ratings of 3 across more than three consecutive intervention days.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by the PI and Co-I Caspari based on temporal relationship and their judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – There is a reasonable possibility that the study procedures caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the AE.

8.3.3.3 EXPECTEDNESS

The PI and Co-I Caspari are responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or upon review of data.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while in the study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AE monitoring occurs in weeks 2-3 and 5-6 when intervention is provided.

8.3.5 ADVERSE EVENT REPORTING

Adverse events (AEs) will be reported to the IRB within 5 business days in writing (e-mail) by the PI. AEs include consistent high frustration levels (scores of 2 or 3 across more than three consecutive intervention days) and unanticipated AEs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events (SAEs) will be reported to the IRB immediately upon discovery with a brief report, followed within 5 business days by a more detailed report in writing (e-mail) by the PI. SAEs will also be reported to NIH in consultation with the IRB within 10 business days. No SAEs are anticipated in this trial.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Parents will be notified by the PI and/or Co-I Caspari about any AEs or SAEs recorded for their child.

Results of testing will be shared with children's parents but not with others, unless parents provide explicit written permission to share this information (for example, with clinical service providers such as

speech-language pathologists or audiologists). We provide parents with a report of the test results, which may aid in educational or clinical planning for the children. The PI and/or Co-I Caspari will discuss any incidental findings and interpretation of findings with the parents.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems may include children being unable to complete required tasks, receiving the wrong intervention condition, data breach, and participant complaints. Appropriate action will be taken to prevent these problems going forward, and may include

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures

- Suspension of consenting/enrollment of new participants or halting of study procedures for consented/enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously consented/enrolled participants.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB immediately upon discovery and in writing within 5 business days, and to NIH within 10 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 5 business days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) promptly but within 10 business days of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Parents will be notified by the PI and/or Co-I Caspari about any UPs for their child as soon as possible.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

9.1.1 STUDY 1: ASSIST VS. NO (DELAYED) ASSIST

ASSIST Hypothesis: ASSIST improves speech motor planning skills in CAS. This is expected to improve perceptual speech accuracy, intelligibility, confidence, and communicative participation.

> *ASSIST Prediction*: Greater improvement (change score from T1 to T2_ for children who have received ASSIST than for children who have not (yet) received ASSIST.

Null Hypothesis: ASSIST does not improve speech motor planning skills in CAS.

> *Null Prediction*: No difference in change score from T1 to T2 for children who have received ASSIST and children who have not (yet) received ASSIST.

9.1.2 STUDY 2: SIMPLE ASSIST VS. COMPLEX ASSIST

Simplicity Hypothesis: Children with CAS learn more effectively with simple targets. Simpler sounds and syllables foster early success and enable the child to build longer, more complex movement plans by combining basic building blocks.

> *Simplicity Prediction*: Greater improvement (change score from pre to post) for children who receive Simple ASSIST than children who receive Complex ASSIST.

Complexity Hypothesis: Children with CAS learn more effectively with complex targets. Complex targets provide more practice with integrating and sequencing movement components, allowing children to extract more information about the underlying speech motor skill; complex targets also may subsume simpler movements which therefore receive practice as well.

> *Complexity Prediction*: Greater improvement (change score from pre to post) for children who receive Complex ASSIST than children who receive Simple ASSIST.

Null Hypothesis: There are no effects of complexity of ASSIST on speech motor learning in CAS.

> *Null Prediction*: No difference in change score from pre to post for children who received Simple ASSIST and children who received Complex ASSIST.

9.1.3 STUDY 3: WORD ASSIST VS. NONWORD ASSIST

Word Hypothesis: Children with CAS learn more effectively with existing words than with nonwords. Real words enhance motivation due to their communicative relevance; real words may also receive practice outside the treatment setting.

> *Word Prediction*: Greater improvement (change score from pre to post) at 1 week post treatment for children who receive Word ASSIST than children who receive Nonword ASSIST.

Nonword Hypothesis: Children with CAS learn more effectively with nonwords. Nonwords require activating and assembling novel motor plans, instead of relying on retrieving pre-existing, possibly incorrect speech motor plans and semantic activation; nonwords also allow for more systematic and controlled variation of phonetic context.

> *Nonword Prediction*: Greater improvement (change score from pre to post) at 1 week post treatment for children who receive Nonword ASSIST than children who receive Word ASSIST.

Null Hypothesis: There are no effects of lexicality of ASSIST on speech motor learning in CAS.

> *Null Prediction*: No difference in change score from pre to post for children who received Word ASSIST and children who received Nonword ASSIST.

9.1.4 STUDY 4: MASSED ASSIST VS. DISTRIBUTED ASSIST

Distributed Hypothesis: Children with CAS learn more effectively with distributed than with massed treatment. Distributed practice results in more forgetting, and requires more, deeper processing for the next attempt (reconstructing the movement from scratch), resulting in more detailed movement plans.

> *Distributed Prediction*: Greater improvement (change score from T1 to T3) for children who received Distributed ASSIST than for children who received Massed ASSIST.

Massed Hypothesis: Children with CAS learn more effectively with massed than with distributed treatment. Massed practice facilitates neuroplastic processes (e.g., synaptogenesis) which in turn support sustained behavioral performance improvements (i.e. learning).

> *Massed Prediction*: Greater improvement (change score from T1 to T3) for children who received Massed ASSIST than for children who received Distributed ASSIST.

Null Hypothesis: There are no effects of intensity of ASSIST on speech motor learning in CAS.

> *Null Prediction*: No difference in change score from T1 to T3 for children who received Massed ASSIST and children who received Distributed ASSIST.

9.1.5 STUDY ENDPOINTS (FOR STUDIES 1-4)

Primary Endpoint

- *Primary Endpoint*: Perceptual speech accuracy of treated targets at 1 week post treatment. Improved speech motor planning skill is expected to improve speech accuracy.

Secondary Endpoints

- *Secondary Endpoint 1 (SE-1)*: Perceptual speech accuracy of full 30-item target set at 1 week post treatment. Improved speech motor planning skill is expected to improve speech accuracy.
- *Secondary Endpoint 2 (SE-2)*: Intelligibility-in-Context Scale (ICS; McLeod et al., 2012) mean total score at 1 week post treatment. Improved speech accuracy and speech motor planning skill are expected to improve intelligibility in the child's everyday life, as reflected in the caregiver-reported ICS.
- *Secondary Endpoint 3 (SE-3)*: Focus on Outcomes of Children Under Six (FOCUS-34) (Thomas-Stonell et al., 2012) mean total score at 1 week post treatment. Improved speech accuracy and speech motor planning skill are expected to improve intelligibility and communicative confidence, which together are expected to improve communicative participation, as reflected in the caregiver-reported FOCUS-34.
- *Secondary Endpoint 4 (SE-4)*: Mean percentage intelligibility based on the Test of Children's Speech (TOCS+) (Hodge et al., 2009, 2012, 2014a,b) at 1 week post treatment. Improved speech motor planning skill and accuracy are expected to improve intelligibility, as reflected in TOCS+ intelligibility.

9.2 SAMPLE SIZE DETERMINATION

As a Phase 1 trial of a novel treatment, this study is not powered to detect a definitive effect. Instead, realistic sample sizes for a summer camp at a single site were used to estimate effect sizes and sample sizes to test the hypotheses described in the previous section (***Section 9.1, Statistical Hypotheses)***. Findings from this trial will inform effect size estimates to determine sample sizes to power subsequent Phase 2 and Phase 3 trials and determine the need for multisite trials. Estimates below are for the primary endpoint of perceptual speech accuracy of treated targets, computed using G*Power (Faul et al., 2007); no power estimates were computed for secondary outcome measures.

For the primary endpoint of Study 1 (perceptual speech accuracy) to test the primary hypothesis (*ASSIST Hypothesis*), with a sample size of 40 children (n=20 per condition, ASSIST vs. No ASSIST), $\alpha = 0.05$ (two-tailed), we expect to have at least 80% power to detect an ASSIST treatment effect size (mean difference between groups over the study period, divided by the pooled standard deviation) of 0.909 using a two-sample t-test. The only prior randomized controlled trial for CAS (Murray et al., 2015), with 26 children

enrolled, reported effect sizes of 1.312 and 2.162 with only 12 hours of treatment (two different treatments), suggesting that the present study will have sufficient power to detect effects. See ***Table 2*** below for estimates of remaining power with different numbers of participants (e.g., in case of under enrollment, attrition).

Table 2. Estimated power to detect effect size of 0.909 for Study 1.

Total *N*	*n* per group	Statistical power
40	20	80%
38	19	77%
36	18	75%
34	17	72%
32	16	70%
30	15	67%

For Studies 2-4, with sample sizes of 20 children per study (n=10 per condition), $\alpha = 0.05$ (two-tailed), we expect to have at least 80% power to detect condition/intensity treatment effect sizes of 1.325 using a two-sample t-test. See ***Table 3*** below for estimates of remaining power with different numbers of participants (e.g., in case of under enrollment, attrition).

Table 3. Estimated power to detect effect size of 1.325 for Studies 2-4.

Total *N*	*n* per group	Statistical power
20	10	80%
18	9	75%
16	8	69%
14	7	62%
12	6	54%
10	5	45%

9.3 POPULATIONS FOR ANALYSES

Modified Intention-to-Treat (ITT) analysis will be used to statistically analyze the results (i.e., all randomized participants who received at least one session of the intended ASSIST intervention). Per-Protocol analysis will be used in the event that a participant changes intervention condition.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Descriptive statistics (e.g., mean, median, standard deviation, skewness, and frequencies) will be computed for all variables to ensure data quality and evaluate assumptions of statistical tests. We will

compare the pre-treatment performance between groups (ASSIST/No-ASSIST, Simple/Complex, Word/Nonword, Massed/Distributed) to assess the success of randomization in producing two comparable groups. Although we do not expect any imbalances between groups, we will adjust for any differences in our subsequent analyses to be sure any treatment effect is not due to potential confounds. For all analyses, we will use Statistical Analysis Software (SAS, v9.4, Cary, N.C.), with two-sided tests under presumed significant level of 0.05.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoint measure is change score from 1 week pre to 1 week post treatment for the populations described above in ***Section 9.3, Populations for Analyses***. For perceptual accuracy, at least two independent data analysts (blinded to timepoint, treatment status, condition, and targets) score each target on a ordinal 3-point scale. Mean across the data analysts for each target is then used to compute the mean across treated targets (primary endpoint) and across the full 30-item target set (secondary endpoint 1) for each timepoint (T1, T2, T3). Means are converted to percentage accuracy by dividing means by 2. Finally, difference scores are then computed by subtracting the relevant pre-treatment timepoint from the relevant post-treatment timepoint. These change scores are the primary endpoint variable entered into the analyses described below and will be reported as means with standard error.

To address the effect of ASSIST (the *ASSIST Hypothesis,* Study 1), independent two-sample t-tests will be used to compare change scores (T2 – T1) between the Immediate ASSIST group and the No ASSIST delayed control group (combined sample across Cycles 1 and 2). A separate linear model will be fitted by adjusting for potential effect of study (Cycle 1/Cycle 2) to re-assess the initial efficacy of ASSIST.

To address the effect of complexity (*Simplicity vs. Complexity Hypothesis*, Study 2), independent two-sample t-tests will be used to compare change scores between conditions (i.e., Simple/Complex). Change scores will be based on T2 – T1 for the Immediate ASSIST group and T3 – T2 for the Delayed ASSIST group. Separate linear models will be fitted by adjusting for potential effect of ASSIST delivery time (Immediate/Delayed) to re-assess the effect of complexity.

To address the effect of lexicality (*Word vs. Nonword Hypothesis*, Study 3), independent two-sample t-tests will be used to compare change scores between conditions (i.e., Word/Nonword). Change scores will be based on T2 – T1 for the Immediate ASSIST group and T3 – T2 for the Delayed ASSIST group. Separate linear models will be fitted by adjusting for potential effect of ASSIST delivery time (Immediate/Delayed) to re-assess the effect of lexicality.

To address the effect of intensity (*Massed vs. Distributed Hypothesis*, Study 4), independent two-sample t-tests will be used to compare gain scores (T3 – T1) between the Massed ASSIST group and the Distributed ASSIST group. Because the Massed ASSIST group combines both *Immediate* Massed and *Delayed* Massed groups, no additional models will be fitted by adjusting potential effect of ASSIST delivery time (Immediate/Delayed) to re-assess the effect of intensity.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analysis of secondary endpoints (see ***Section 9.1, Statistical Hypotheses***) is not dependent on findings for the primary endpoint. Analysis of secondary endpoints is as described above for the primary endpoint (***Section 9.4.2, Analysis of the Primary Endpoint(s)***).

For Secondary Endpoint 1 (perceptual accuracy of full 30-item target set), perceptual accuracy analysis procedures are as described above for the primary endpoint. For Secondary Endpoint 2 (ICS) and Secondary Endpoint 3 (FOCUS), we use mean score across items. For Secondary Endpoint 4 (TOCS+), we use the mean percentage accuracy across listeners. Variables entered into analyses are change scores computed based on the same timepoints as for the primary endpoint as described above (***Section 9.4.2, Analysis of the Primary Endpoint(s)***). No imputation will be used for any missing data.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

We will compare the pre-treatment performance between groups in each study to assess the success of randomization in producing two comparable groups. Although we do not expect any imbalance between groups, we will adjust for any differences in subsequent analyses to be sure any treatment effect is not due to potential confounds.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Sex as a biological variable will be included in all analyses, though we do not expect any sex differences.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point.

9.4.9 EXPLORATORY ANALYSES

N/A

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms (Parent Permission Form, PHI Authorization Form) describing in detail the study intervention, study procedures, and risks are given to the parent and informed consent will be documented in writing prior to starting study screening and intervention. A Study Information Sheet is used to guide age-appropriate explanation of the purpose of the study and obtain verbal assent. The following consent materials are submitted with this protocol

- Parent Permission Form
- Personal Health Information (PHI) Authorization Form
- Child Study Information Sheet

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

After initial contact and before their first appointment, parents receive (via e-mail or regular mail) a copy of the Parent Permission Form, a Study Information Sheet for children, and a Personal Health Information Authorization Form, to allow them to read these forms over at their leisure, discuss this opportunity at home, and generate any questions prior to the first visit.

At the first appointment, parents are provided with the Parent Permission Form. Research personnel verbally explain the form to parents and answer any questions they have. Parents who agree to the conditions described in the Parent Permission Form are asked to sign the forms. Permission is obtained from only one parent because the risks associated with this research are considered minimal. Permission may be obtained from a legal guardian if appropriate; we will require written documentation affirming the legal ability to consent to the child's general medical care; this documentation will be kept with consent documents.

The study is then explained verbally to the child in age-appropriate language using the Study Information Sheet, and questions are encouraged to ensure understanding. Children capable of giving assent will be also be asked to sign the Study Information Sheet. Per local IRB policy, clear positive affirmation by the child of assent to participate is documented by a check mark on the Parent Permission Form confirming the child's assent. Next, because we collect personal health information, parents are given a Personal Health Information Authorization Form. The purpose of this form is explained, and any questions are answered. If they agree, they are asked to sign the form. Parents receive copies of these forms for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the Principal Investigator (PI) to study participants, IRB, and funding agency (NIH).

Study procedures, including intervention, may be discontinued for all participants under the following circumstances:

- Determination of unexpected, significant, or unacceptable risk to participants. In this trial, this refers to child frustration experienced during ASSIST intervention sessions. In this minimal risk study, we do not anticipate any significant adverse events. However, if 10 or more children in Cycle 1 or 2 experience recurrent significant or marked frustration (as described above in ***Section 7.1, Discontinuation of Study Intervention/Experimental Manipulation***), subsequent cycles will not be initiated regardless of whether children withdraw (e.g., if 10 or more children with significant or marked frustration in Cycle 1, then Cycle 2 will not be initiated).
- Data that are not sufficiently complete and/or evaluable. Although unlikely, children may withdraw from the study, either because of recurrent frustration with study procedures or for other reasons. In the highly unlikely event that withdrawals exceed 5 children in any year, the research team will discuss what, if any, action should be taken to improve retention and whether to discontinue the study.
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency and IRB.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant is held in strict

confidence within the research team. No personally-identifiable information from the study is released to any unauthorized third party without prior written approval of the participant.

All research activities will be conducted in as private a setting as possible. Children are tested and receive treatment individually. However, because the study is conducted in the format of a camp, children and parents interact with other children and parents. Research personnel will use names for pragmatic reasons, but will share no other PHI with other children or parents.

Participants are assigned a unique ID code. The master list linking participant names and ID codes will be stored in an encrypted password-protected electronic file on the HIPAA-compliant server; a hard copy of the master list will be stored in a locked filing cabinet in a locked room. Only the Investigator and appropriate research personnel will have access to the master list on an as-needed basis.

Any identifiable data will be accessible only to qualified research personnel for research purposes and will not be shared with others, unless participants or parents provide explicit written permission to share this information (for example, to share with clinical service providers). We will provide parents with a report of the test results, which may aid in educational or clinical planning for the children. Data from this research may be used in publications and presentations, but participants will only be identified by their ID code. Audio and video recordings will only be used with authorization and for the purposes indicated on the Parent Permission Form and will never include names, addresses, or other identifying information (except for voice recording or facial images). Authorized representatives of the funding agency and the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to background testing and treatment progress notes for the participants in this study.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

All paper-based PHI information is stored in locked filing cabinets in locked rooms, and all electronic PHI is stored in encrypted password-protected files on a HIPAA-compliant server accessible only via password-protected computers. Data will be retained until the participant/parent requests in writing that data be destroyed, or until seven years after the final publication resulting from this study or until seven years after the child turns 18, whichever occurs later. All information, past and current, will be used only for purposes authorized on the Parent Permission Form. The potential uses of audio and video recordings of children (in addition to research purposes) include scientific presentations and publications, non-scientific presentations and publications, and teaching purposes

Parents and participants will be informed of all these procedures, both in person (verbally) and in writing on the Parent Permission Form. They will be informed that they may change their mind or revoke authorizations in writing at any time. Further, they will be told that they may choose to not answer any questions that they do not feel comfortable answering.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms

used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be stored and retained on the HIPAA-secure server hosted by Temple University. After the study is completed, the de-identified data set will be made available for use by other interested researchers, speech-language pathologists, and members of the general public upon request after submitting to the PI a data sharing agreement. Permission to make these data available is included in the informed consent. Parents are informed that they may change their mind or revoke authorizations in writing at any time.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	
Name, degree, title	Edwin Maas, PhD, Associate Professor & SLAB Lab Director
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10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI, in consultation with Co-I Caspari, the SLP supervisors, and the treating SLPs. This team will meet at the end of every intervention day.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed*.*

Source documents and the electronic data --- Data will be initially captured on source documents (see ***Section 10.1.9, Data Handling and Record Keeping***) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in ***Section 6.2.1, Interventionist Training and Tracking***.

Data Collection Fidelity – The Data Collection team will receive extensive training on the data collection protocol, including a written manual, role play examples, recording equipment familiarization, and data backup. Data collection sessions are recorded (audio & video) and supervised in real time via secure video feed by the PI or Project Manager. Data Collection protocol deviations are reviewed on an ongoing basis and corrective actions will be implemented as needed.

Data Analysis – The Data Analysis team will receive extensive training on the data analysis protocol, including a written manual, playback software familiarization, and data backup. Data analysts first complete a calibration stage during which they score data from children with CAS (from prior studies in the lab). Once calibrated, all responses by all children are scored by at least two analysts and inter-rater reliability is assessed.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All data will be stored as described above (see ***Section 10.1.3, Confidentiality and Privacy***). For the purpose of determining study eligibility based on presence of CAS, video recordings of clinical evaluation sessions (screening) are shared with external SLP experts (Drs. Gildersleeve-Neumann &

Stoeckel) via Temple University's SafeSend file sharing system (see ***Section 8.1, Endpoint and Other Non-Safety Assessments***).

Source data include:

- Clinical evaluation score form and notes from screening
- Tracking sheets and clinical notes from intervention sessions
- Audio and video recordings of evaluation sessions
- Audio and video recordings of intervention sessions
- Audio and video recordings of data collection sessions
- Parent-reported questionnaires and outcome measures
- Spreadsheets with outcome data

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained until the participant/parent requests in writing that data be destroyed, or until seven years after the final publication resulting from this study or until seven years after the child turns 18, whichever occurs later.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

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

It is the responsibility of the PI to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations will be addressed in study source documents, and reported to the NIDCD Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The PI will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations, including the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers within 1 year of the completion of the primary endpoint by contacting the PI. Considerations for ensuring confidentiality of these shared data are described in ***Section 10.1.3, Confidentiality and Privacy***).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ASHA	American Speech-Language-Hearing Association
ASSIST	Apraxia of Speech Systematic Integral Stimulation Treatment
CAS	Childhood Apraxia of Speech
CAS3SLP	Childhood Apraxia of Speech 3 Speech-Language Pathologists' diagnostic rating scale
CELF	Clinical Evaluation of Language Fundamentals
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
Co-I	Co-Investigator
CRF	Case Report Form
CSD	Communication Sciences and Disorders

CTOPP	Comprehensive Test of Phonological Processing
CV	Consonant-Vowel
DEAP	Diagnostic Evaluation of Articulation and Phonology
DEMSS	Dynamic Evaluation of Motor Speech Skill
DHHS	Department of Health and Human Services
EVT	Expressive Vocabulary Test
FB	Feedback
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FOCUS-34	Focus on Outcomes of Communication Under Six
FRS	Frustration Rating Scale
GCP	Good Clinical Practice
GFTA	Goldman-Fristoe Test of Articulation
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
ICC	Intra-class correlation
ICF	International Classification of Functioning and Disability
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ICS	Intelligibility-in-Context Scale
IPC	Index of Phonetic Complexity
IRB	Institutional Review Board
ITT	Intention-To-Treat
KP	Knowledge of Performance
KR	Knowledge of Results
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OME	Oral mechanism examination
PI	Principal Investigator
PPVT	Peabody Picture Vocabulary Test
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
RIAS	Reynolds Intellectual Assessment Scales
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SCED	Single-Case Experimental Design
SD	Standard Deviation
SLAB Lab	Speech, Language, and Brain Laboratory
SLP	Speech-Language Pathologist
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SRT	Syllable Repetition Task
T1,T2,T3	Timepoints 1, 2, and 3
TE	Teaching Episode
TOCS+	Test of Children's Speech Intelligibility
TU	Temple University
TUSLHC	Temple University Speech-Language-Hearing Center
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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