**Title: New Tool to Enhance Post-stroke Upper Extremity Disability**

Study Protocol, Statistical Analysis Plan, and Informed Consent form

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**Study Protocol & Statistical Analysis Plan**

We will conduct a stratified, parallel-group, double-blind, randomized controlled trial of remotely delivered START treatment to individuals with severe-to-moderate stroke (with recruitment focused on individuals with low SES). Subjects and assessors will be blinded to the condition making the experiment double blind. Specifically, subjects will be told that we are exploring a new therapy that using different sounds to improve therapy. Parallel group design will ensure that subjects in the Control group are unaware that their "sounds" are softer than the START group. Trainers may become aware that a loud sound is present thus unique Assessor will evaluate clinical performance before and after training. Assessor will be a certified and practicing occupational therapist.

Fifty-eight subjects will undergo baseline testing in the laboratory to establish their upper extremity impairment, spasticity, and function as well as their self-reported health-related quality of life. Next, subjects will participate in high-repetition training, 2 hr/day for 3 consecutive days focusing on functional object manipulation (details below). Subjects will either receive training with START or without (Control). Subjects will be re-tested immediately following training as well as one-month post to assess retention. Activity trackers will be deployed before (baseline), during, and after training. Aim 1 will evaluate the ability of START to enhance therapy outcomes by assessing the % change clinical assessment of function, spasticity, impairment, and self-reported quality of life, functional independence, and arm usage. Aim 2 will focus on the capacity of these changes to 1) be retained and 2) impact subject's self-reported quality of life. *NOTE:* While we are planning in-person baseline, end, and retention testing, in response to covid, we have established remote clinical screening (see Potential Challenges and Solutions).

Study population and screening: A diverse set of individuals with stroke-induced upper-extremity paresis will be recruited consistent with the 2010 census results (Non-Hispanic white: 69%, Hispanic: 12.5%, African American: 12.3%, Asian: 3.6%, and American Indian: 0.9%). We will include equal numbers of males/females to further examine possible sex differences in treatment effects. As this proposal is geared at reducing post-stroke disparity in individuals with low SES, we put an emphasis on recruiting in this population (see Retention and Recruitment).

**Table 1: Recruitment Criteria**

**Inclusion Criteria**

1) >18 years old
2) Capacity to provide informed consent
3) Cerebral stroke at least 6 months prior to testing
4) Presence of severe-to-moderate upper extremity impairment (UEFM < 42/66)
5) Corrected pure tone threshold (octave frequencies 250- 4000 Hz) norms for their age and gender[27,28] **NOTE**: Audiometry data will be collected for all participants by lab personnel trained by an audiologist in a sound-attenuated booth. We expect that ~30% of participants will use hearing aids; we will not exclude these individuals but rather include hearing aid use as a covariate in analyses.

**Exclusion Criteria**

6) Severe concurrent medical problems (e.g. uncontrolled cardiorespiratory impairment)
7) Acute/painful condition/injury of upper

Recruitment will proceed through 1) our multi-site collaborative registry of stroke survivors, 2) Barrow Neurological Institute's NeuroRehabilitiation Clinics, and 3) Banner Medical University Hospital. The PI has used these sources for recruitment of stroke participants for the preliminary data for this project and for K99/R00HD073240. Based on our recruitment history, we expect to screen ~80 potential participants each year, 50 of whom we expect will fit all of our criteria and participate, with ~15% attrition.

After being recruited, subjects will be first interviewed to determine their eligibility (**Table 1**). If they meet the criteria, they will come to the lab to complete baseline testing.

**Baseline Testing:** Baseline testing will include biometrics, stroke injury information, clinical assessment of impairment, spasticity, and function, and patient health-related quality of life (see below). To confirm the stroke injury, recent and/or admittance MRIs, as well as radiology and neurology reports, will be used to confirm date, location, and type of stroke (e.g. ischemic, hemorrhagic). Biometric data (e.g., height, weight, demographics). Hearing tests will be administered (see inclusion criteria); however, it is

notable that the START effect has been observed in individuals with hearing loss[14,18]. We will closely monitor and if needed include hearing capacity in statistical models.

To assess impairment, function, and spasticity stroke participants will complete standard clinical assessments.

(1) *Impairment*: The Upper-Extremity Fugl-Meyer (FMA-UE) will used to quantitatively evaluate impairment. The FMA-UE is one of the most commonly utilized measure of impairment both in clinical and research settings. It has excellent interrater and retest reliability. Severe-to-moderate impairment will be defined as <42/66.
(2) *Function*: The Action Research Arm Test (ARAT) will be used to quantify upper extremity function, coordination, and dexterity during tasks relevant to activities of daily living. Nearly all tasks have excellent internal consistency in addition to excellent test/retest and interrater reliability.
(3) *Spasticity*: Due to high variability in test/retest and inter/intra-rater reliability, two tests will be administered to assess spasticity of the shoulder (ab/adduction) elbow (flex/extension), wrist (flex/extension), thumb (flex/extension), and hand (all digits – extension): Modified Ashworth (MA) and Modified Tardieu Scale (MTS). While MA is the more commonly administered test, it suffers from moderate/weak interrater reliability. The MTS, which is similar to the Ashworth but makes use of goniometers, has excellent test/retest reliability as well as interrater reliability. The modified Tardieu also includes Passive Range of Motion (PROM) which can be assessed independently.

To assess patient's health-related quality of life, we will administer the following generic preference-based measures (GPMs).

(1) The Stroke Impact Scale (SIS) is a self-report scale of disability and health-related quality of life. We will use the subdomains of hand function, ADL/IADL, and mobility. These domains have excellent test/retest reliability and excellent (hand function, mobility) or adequate (ADL/IADL) inter/interrater reliability. All tested domains also have excellent internal consistency.
(2) Modified Rankin (MRS) is a patient reported outcome that categorizes functional independence with reference to pre-stroke activities. It has excellent test/retest and inter/intra-rater reliability.
(3) Motor Activity Log (MAL) is a semi-structured interview of patient reported arm function. It has excellent test/retest reliability and internal consistency.

**Training protocol:** During the baseline assessment, subjects will be given a training kit (**Fig 2**). The training kit includes: a phone (Pixel 2 - Google, Mountain View, CA; OS: Android 10, Chipset: Qualcomm MSM8998 Snapdragon 835) and headphones (JLab studio - JLab Audio, Carlsbad, CA; Drivers: 40mm neodymium; Frequency: 20Hz-20kHz) with a microphone which acts as a backup for audio recordings. The phone comes with a preloaded, custom-built, app developed using android studio with Java for functionality and Extensible Markup Language for the user interface. It can deliver randomly applied sounds per the specifications below and display recorded files and playback using a media player. The app is controlled remotely by the Trainer/Experimenter using AnyDesk App for Android (AnyDesk Software GmbH, Germany); thus, the phone app is controlled remotely by the experimenter. Subjects or caretakers are only responsible for charging the phone and do not have to perform any other actions to manipulate the phone. Further, this ensures that subjects cannot be exposed to loud, startling sounds unless explicitly delivered by the trainer.

Subjects will receive 3 consecutive days of remote, telehealth sessions via secure video service. Upper extremity therapy for individuals with severe impairment focuses on tasks of functional significance e.g., self-feeding. For consistency across subjects and to allow statistical comparison, we have chosen 3 tasks

related to self-feeding: hand extension, object lifting, and arm extension. For the hand extension task, subjects will be seated in front of an unopened, full, soda can. They will be asked to open their hand to grab the soda can. For object lifting, subjects will be asked to lift the soda can to their mouth. If they cannot grasp the can voluntarily or if it is too heavy, they will be assisted or given a small, light block or no object if necessary. Empty soda cans are often crushed by high hand spasticity in individuals with severe stroke; thus, a rigid object (e.g., block is used). For the arm extension task, a soda can will be placed at 80% arm's length away from the subject's body. Subjects will be asked to attempt to reach the soda can and touch it with their hand (grasp if able).

Practice of these tasks will be modified to be amenable to the START protocol. Specifically, subjects will practice attempting each task following two non-startling (80dB SPL) acoustic cues. The first acoustic cue will indicate "get ready." The second acoustic stimulus will indicate "move". During START training, the "move" cue will be randomly replaced with a startling, acoustic stimulus of ~120dB over 0.04s. To reduce anticipation, which is required for a consistent START response, the startling stimulus will be applied during only 33% of trials. This protocol has been well established for generating the highest percentage of startles[24]. Each of the 5 training days, subjects will practice each task 45 times with 15 trials accompanied by the startling, acoustic stimulus. The Control group subjects will practice each task the same amount of times (45) but none of the trials will include the startling, stimulus.

**End- and Retention- Testing**: The same measures (except biometrics) evaluated during Baseline assessment (FMA-UE, ARAT, MA, MTS, SIS, MRS, MAL) will be collected on the final day of training as well as one-month post training. Finally, a questionnaire about START will be administered asking about ease of use, comfort, adverse side effects (none have ever been reported).

***Analysis for Aim 1:*** **To establish that START can increase functional paretic limb usage, we will perform a randomized controlled trial assessing the impact of START on therapy outcomes.**

We hypothesize that training with START will increase paretic arm function (ARAT), self-reported arm function (MAL), and functional independence (mRS) compared to training without START. To assess this, we will evaluate effects of the treatment (START vs control) on a group of random subjects from a parallel group of stroke patients. The hypothesis expects a positive impact over multiple days of evaluation with respect to the baseline. We do not expect the data to conform to Gaussian norms. Therefore, we will utilize a generalized linear mixed model to identify differences between groups in this longitudinal data set. The *treatment* (START vs. control) and the *day of testing* (pre, post) will be setup as the fixed factors. *Subjects* will be treated as a random factor, nested within treatment. Tukey post-hoc tests will be employed with a p-value <0.05 will be used to indicate significance. Analysis will be conducted using R's lme4 package[25].

***Analysis for Aim 2:*** **To establish that START generates retainable changes that impact quality of life, we will re-assess upper-extremity function and self-reported quality of life (SIS, MRS).**

We hypothesize that A) START gains will be retained more than Control and B) retention will be associated with higher quality of life measures (e.g., SIS) one-month post-START training. For A, the same analysis as proposed above will be conducted except the *day of testing* will compare post-training to one-month post as the fixed factors. To complete the analysis for B, we will utilize a regression analysis between the change in the functional score and the change in the quality of life for each subject. The choice between a linear and a logistic regression will be determined by the data themselves. Analysis will be conducted in R, using the base R functionality.

Consent Form: Bioscience

**Title of research study:** The use of startle-evoked movement to evaluate reach and grasp (Hybrid Study)

**Investigator:** Claire Honeycutt, Ph.D

**Why am I being invited to take part in a research study?**

You are being asked to be a subject in a research study about movement planning and learning. Our objective is to understand how planning and learning is interrupted by neurological disease and injury. You have been asked to participate in the research because you had a stroke so we can understand how an impaired individual performs these tasks.

**Why is this research being done?**

In order to learn a new task, one must develop a cohesive movement plan. We do not understand the time course of this planning process as well as how complex and segmented tasks are planned. Our long-term goal is to develop training programs for individuals with neurological disease and injury

**How long will the research last?**

The research study is conducted in a span of five days split into two parts: 1) Test sessions and 2) Training sessions. Additionally, there will be a one month follow up test session.

Each test session will take 3-4 hours and will occur no more than two times in a week. During these test sessions, the effectiveness of the training is explored by evaluating your ability to reach and grasp objects. Also, you will be asked to partake in an assessment to determine the severity of your impairment. Additionally, there will be a single test session of 3-4 hours one-month after your participation. In total, there will be 3 test sessions.

Each training session will take 1-2 hours, where you will be asked to practice the movements and tasks, that was used for evaluating during the test sessions. These sessions will occur no more than 3 times a week.

**How many people will be studied?**

We expect about 60 people to participate in this research study each year.

What happens if I say yes, I want to be in this research?

It is up to you to decide whether or not to participate.

As a subject in this study, you will be asked to come to a research laboratory in BDH 169 at Arizona State University Tempe campus for each of the test sessions. On the day of first test session, you will receive a telehealth training kit which you can use from your own home for the training sessions. The home sessions with the experimenter will be conducted using a videoconferencing software. You are required to return the training kit to the experimenter when you attend the subsequent test session.

**Pre-Screening Procedures**

To determine if you can take part in the study, you will be asked about past injuries to your arm, your hearing sensitivity, present seizure concerns, and heart conditions which contraindicate exercise related activities. You should not be pregnant during this study. You will also be asked about your ability to participate in telehealth, including questions about the type of computer and videoconferencing software you have access to. In addition, you will also be asked whether you are comfortable and able to participate without assistance from a caretaker. You will also be asked to complete a handedness questionnaire. This will tell us whether you are right- or left-hand dominant.

**Study Procedures**

You will be seated in a comfortable chair for all tasks and assessments. During the test sessions you will have small recording devices called electrodes attached to your skin over several different muscles. These electrodes are similar to stickers but are specially designed to allow us to look at how you use your muscle to perform different tasks. In these sessions you may also have several small non invasive sensors attached to your hand and arm, they will be used to record the kinematic data of your arm and elbow.

Similar to the test session, during the remote training sessions, you will be asked to be seated in your most comfortable chair with a table in front of you, where you comfortably rest your arm. You may be asked to put on an activity tracker on both wrists for the duration of the study. This will be used to record the amount of arm movements you make on a day-to-day basis. During the remote training session, you will be asked to put on the headphones included in the training kit. These headphones will be plugged into the smart phone device, also included in the kit. You will be asked to open an app on the phone that provides the experimenter access to conduct the telehealth training remotely.

The experiment may consist of several tasks using your arm and hand. You will have adequate time to practice these movements and will be allowed to rest in between trials and tasks if you become tired.

Sometimes you may hear a loud, startling sound from the headphones during posturing and preparation of movement. These sounds have been measured to ensure that no hearing damage or injury can occur.

**What happens if I say yes, but I change my mind later?**

You can leave the research at any time it will not be held against you. If you decide to leave the research, there will be no adverse consequences. If you stop being in the research, already collected data may not be removed from the study database. Is there any way being in this study could be bad for me?

*Psychological risks:*

All the devices and equipment used in this research have been used in numerous of research studies and proved to be safe. All precautions will be taken to minimize these risks. Acoustic stimulus may cause temporary discomfort, fatigue and anxiety. If so, you can take a break or withdraw from the study.

*Physical risks:*

Muscle activity and body motion will be recorded using small electrodes placed on the surface of the skin. The skin will be cleansed with alcohol and gently rubbed with a cloth before placing the electrodes on the skin. The skin may show some redness and minor irritation for a few hours after the completion of the experiment.

Physical risks and discomforts expected in this study are dependent on your level of physical fitness. In the days following your participation, you may develop muscle soreness that is common after exercise. Also, the activity tracker worn around your wrist for the duration or the study may cause some slight skin irritation. However, this is like putting on a watch and has been designed to be worn for long hours.

*Privacy risks:*

There is always a potential risk of loss of confidentiality. All data will be labeled with a research code from which subject identification is not possible and only researchers will have access to the codes. All data will be stored on a password-protected hard drive or in a locked cabinet in the laboratory.

**What happens to the information collected for the research?**

Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB, other representatives of this organization, and federal entities that are funding the research.

**What else do I need to know?**

If you agree to take part in this research study, we will compensate you for your time and effort, in the form of an eGiftCard - $100 for the five day testing & training period period and an additional

$50 for the one-month follow-up session. We can provide up to $100 per day to cover transportation costs to testing sites.

In some of the experiments, videotaping may be requested for scientific and professional purposes. Upon your consent, the process of data collection and some experimental detail may be videotaped, but no information in the video record would reveal your identity. The video record will be edited so that your face will not be visible, and the video record will only be used for research purpose. You are also able to stop the videotaping anytime during the experiment.

I give my permission to the investigators to video tape the data collection process and use the edited video recordings, made during the data collection, for professional and scientific purposes. In these edited videos it will not be possible to see my face. **Initial here** _____

I am interested in participating in other studies on campus and I give my permission to the investigators to give my contact information to other researchers who have currently approved IRBs for stroke survivors. **Initial here** _____

**Who can I talk to?**

If you have questions, concerns, or complaints, or think the research has hurt you, contact the PI:

Claire Honeycutt: cfhoneyc@asu.edu

This research has been reviewed and approved by the Bioscience IRB ("IRB"). You may talk to them at (480) 965-6788 or research.integrity@asu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

**Signature Block for Capable Adult**

Your signature documents your permission to take part in this research.

Signature of participant

Date

Printed name of participant

Signature of person obtaining consent Date

Printed name of person obtaining consent