Therapies for Recovery of Hand Function After Stroke

NCT03574623

Study Protocol and Statistical Analysis Plan

Note: The text below was extracted from the IRB protocol for this study, which was first approved on January 22, 2018. The most recent amendment to the protocol was approved on:

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Study Protocol

Abstract

This is the first multi-site clinical trial of contralaterally controlled functional electrical stimulation (CCFES). CCFES is an innovative technology and rehabilitation therapy for improving the recovery of hand function in patients with upper extremity hemiparesis. CCFES applies electrical stimulation to the paretic finger and thumb extensor muscles through surface electrodes, causing the weak hand to open, a function that is often lost in stroke survivors. The patient controls the intensity of stimulation to their paretic hand by wearing a glove with sensors on their unaffected contralateral hand. When the patient opens their unaffected hand, a proportional intensity of stimulation opens their paretic hand. CCFES puts the patient back in control of their paretic hand, and this may drive neuroplastic changes that lead to better recovery of hand function. The central hypothesis is that CCFES is more effective for recovery of hand function than conventional cyclic neuromuscular electrical stimulation (cNMES) therapy or task oriented training (TOT) without electrical stimulation. Stroke survivors between 6 and 24 months post-stroke will be randomized to 12 weeks of CCFES, cNMES (which applies electrical stimulation to the hand extensors but with pre-set timing and intensity), or TOT without electrical stimulation. This study will determine if CCFES can be administered with positive results at other sites, will establish the clinical efficacy of CCFES (comparison with cNMES), and will generate initial estimates of effectiveness of CCFES (comparison with TOT).

Specific Aims

AIM 1. Compare the effects of CCFES and cNMES in improving hand function after stroke.
Research Hypothesis: At 6 mo post-treatment, improvements in hand function will be significantly greater after CCFES than cNMES, and a greater proportion of participants will achieve clinically significant improvements after CCFES than cNMES. Outcomes will include measures of dexterity, upper extremity activity limitation and impairment, and patient-reported outcomes.

AIM 2. Compare the effects of CCFES and TOT in improving hand function after stroke.

Research Hypothesis: At 6 mo post-treatment, improvements in hand function will be significantly greater after CCFES than TOT, and a greater proportion of participants will achieve clinically significant improvements after CCFES than TOT.

Methods and Procedures

This is a 4-site, assessor-blinded Phase II randomized controlled trial to determine whether CCFES is superior to cNMES or TOT in improving hand function in patients with upper extremity hemiplegia who are between 6 and 24 months past their stroke. A target of 132 patients will be randomized to Contralaterally Controlled Functional Electrical Stimulation (CCFES), Cyclic Neuromuscular Electrical Stimulation(cNMES), or Task Oriented Training (TOT). Stratification factors include age, severity of hand impairment, months post-stroke, and treatment site.

All groups will receive 12 weeks of upper limb rehabilitation treatment consisting of a home regimen and functional task practice in the lab. Treatment will include: 1) therapist-administered 90-min sessions of hand task practice twice a week in the lab, and 2) self-administered sessions lasting approximately 1 hour per session 10 times a week at home.

- CCFES group: 90-min 2x/week CCFES therapy with therapist + 10x/week CCFES hand opening exercise self-administered at home.
- cNMES group: 90-min 2x/week therapy with therapist + 10x/week cNMES hand opening exercise self-administered at home.
- TOT group: 90-min 2x/week therapy with therapist + 10x/week home exercise program self-administered at home.

All subjects will be followed for 6 months post-treatment. Blinded assessments will take place at baseline, mid-treatment (6 wk), end-of-treatment (12 wk), and at 3- and 6-months post-treatment.

Baseline characteristics will be collected, including demographic (e.g., sex, age, race, pre-morbid hand dominance), stroke-related (e.g., time post-stroke, hemorrhagic or ischemic, cortical or subcortical, right or left, Stroke Impact Scale score), and neurologic data (e.g., side of hemiparesis, cognition,

depression, neglect, visual deficits, aphasia), as well as co-morbidities, and medications. The balance of these between the three groups and their effect on the outcomes will be evaluated.

The stimulators used in this study for the CCFES and cNMES groups deliver biphasic rectangular current pulses at a pulse frequency of 35 Hz and pulse amplitude of 40 or 60mA. Up to 3 channels of stimulation will be used to produce hand opening. Surface electrodes will be positioned to activate the extensor digitorum communis (EDC) and extensor pollicis longus (EPL). Abductor pollicis brevis (AbPB), dorsal interossei (DI),or extensor indicis proprius (EIP) may also be targeted if they are necessary to achieve functional hand opening. A pulse amplitude (default, 40 mA) and maximum stimulus intensity (pulse duration) will be determined for each stimulus channel so as to achieve maximum finger and thumb extension without discomfort. For the CCFES group, each stimulus channel will be programmed so that stimulation intensities (pulse durations) change in proportion to the amount of opening of a CCFES glove worn on the unaffected hand. The CCFES glove is an assembly of bend sensors (Images SI, Inc., Staten Island, NY) attached to the fingers of an athletic batting glove. For the cNMES group, the stimulator will be set to automatically and repeatedly ramp on and off during an exercise session. After programming the stimulator (for CCFES and cNMES groups), the treating therapist will instruct and train the participants (and their caregivers if necessary), how to put on the components (i.e., electrodes, glove if applicable). The electrodes will be outlined on the skin and photographs of the electrodes correctly positioned will assist the subject in placing them correctly at home. An instruction manual will be reviewed with every participant, and each will be trained how to use their stimulator to complete their exercise sessions at home. Adherence to the home stimulation regimen will be collected with participant diaries and electronic data logging by the stimulator at every visit during the treatment period. From the stimulator's datalogger, the treating therapist will record the number of treatment sessions completed by the participant and the number of stimulated hand openings.

For all groups, treatment will last 12 weeks and consist of: (a) 10 sessions per week of self-administered exercises at home, and (b) 22 sessions of therapist-guided functional task practice in the lab (two per week except on weeks that include an assessment visit). Treatment regimens are:

• CCFES group -- Lab: Observe home-based regimen (15 min). CCFES-mediated functional task practice (75 min). Home: CCFES-mediated cued hand opening exercise(1 session = 22-min set x 2).
• cNMES group -- Lab: Observe home-based regimen (15 min). Functional task practice(75 min). Home: cNMES-mediated hand opening exercise (1 session = 29-min set x 2).
• TOT group -- Lab: Review home exercise program (15 min). Functional task practice(75 min). Home: Home Exercise Program (1 session = 30-min set x 2).

All groups will self-administer 10 exercise sessions per week at home. Each participant should do no more than 2 sessions per day separated by at least 2 hours; on days they come to the lab for a treatment session, they should do no more than one home session. The treating therapist and participant will create a schedule each week that helps the participant know when they should do their 10 exercise sessions for that week. Each home exercise session will consist of 2 exercise sets separated by 3 min of rest. For CCFES and cNMES groups, each set consists of repeated stimulation-mediated hand opening. For the CCFES group, the stimulation-mediated hand opening will be cued by audio and visual prompts. During the first two weeks, the cues will prompt the CCFES participants to open both hands at the same time and maintain hand opening for 6 seconds then rest for 14 seconds, repeating this for the duration of the set. At week 3, the treating therapist will change the cue timing to 8 sec open, 12 sec rest; at week 5 it will again be changed to 10 sec open, 10 sec rest. For the cNMES group, the stimulator will turn on and off automatically according to the same timing as the cues for the CCFES group; this will produce an automatic repetitive cycle of hand opening and resting for the cNMES group. For the TOT group, a home session will consist of practicing using the paretic hand to perform a list of tasks for several minutes each as instructed in the lab, and/or self-administering active-assisted range of motion and activities in preparation for hand tasks.

Each of the twenty-two 90-min lab sessions will begin with 15 minutes of the treating therapist observing the participant performing the exercise they do at home, reinforcing instructions, and troubleshooting any problems, followed by 75 minutes of instructing and guiding the participants in practicing functional tasks with their paretic hand. Tasks will involve using the paretic hand to pick up, manipulate, and release objects commonly used in daily life. The treating therapist will adjust task difficulty from easy-to-acquire-and-manipulate tasks to tasks requiring wider hand opening, greater

complexity and skill, graded hand opening (release), and coordination of hand function with proximal upper limb movement. The pace and content of the therapy will be standardized via study-specific protocols and task lists. The CCFES group will use CCFES to assist the paretic hand in performing tasks. The cNMES group will practice tasks using their paretic hand but without any stimulation because cNMES is not amenable to assisting with tasks since it is not controlled by the patient (one of the unique advantages of CCFES). Therefore, to ensure that both groups receive an equal weekly duration of electrical stimulation, the cNMES group will have longer home stimulation exercise sessions than the CCFES group (see treatment regimens above). The TOT group will receive the same task practice as the cNMES group (i.e., no stimulation). For subjects with severe hand impairment, early task practice sessions will focus on simpler tasks, such as opening the hand adequately to acquire a small object. If it is not possible to perform tasks, then the therapist will focus on passive and active-assisted range of motion, arm placement activities in preparation for hand tasks, and hand placement on target surfaces and objects.

Adherence to the home stimulation regimen will be monitored with participant diaries and electronic data logging by the stimulator at every visit during the treatment period. The stimulator logs the date and time the unit is turned on and off and the start and completion of exercise periods. All participants will also be given a diary to log completion of sessions. The diaries will be reconciled with electronic data logs at every lab session, in the presence of the participant to encourage adherence.

Outcome Measures

Blinded assessments will take place at baseline, mid-treatment(6 wk), end-of-treatment (12 wk), and at 3- and 6-months post-treatment. All assessments will be done with no electrical stimulation. Subjects will refrain from using their stimulators for 24 hours prior to their 6-week and 12-week assessments in order to avoid any transient carry over effects or muscle fatigue.

Box and Blocks Test (BBT): The primary endpoint is change in dexterity at 6-monthspost-treatment, as assessed by the BBT. The BBT is a measure of manual dexterity, which requires the subject to pick up one block at a time, move it over a partition, and release it in a target area as many times as

possible in 60 seconds. Participants will perform the test first with the unaffected hand, and then with the affected hand. The BBT is classified as an activity (ICF domain) measure by the Rehabilitation Measures Database and the Evidence-Based Review of Stroke Rehabilitation.

Upper Extremity Fugl-Meyer Assessment (UEFM). The UEFM is a measure of post-stroke upper limb motor impairment that takes into account synergy patterns, isolated strength, coordination, and hypertonia. Volitional movement of the upper limb (shoulder, elbow, forearm, wrist, and hand) is examined in and out of synergies. Each item is graded on a 3-point ordinal scale (0, cannot perform; 1, perform partially; and 2, perform fully) and summed to provide a maximum score of 66.

Action Research Arm Test, (ARAT): The ARAT is a measure of upper extremity functional ability. The ARAT is a 19-item test divided into four categories (grasp, grip, pinch, and gross movement), with 16 of the 19 ARAT items measuring distal regions of the arm, making it an ideal and sensitive measure for this distally based intervention.

Stroke Upper Limb Capacity Scale (SULCS). The SULCS is a 10-item test in which stroke patients are rated using a 2-point ordinal scale on their performance of upper limb tasks ranging from reaching forward to manipulating coins. It is a valid and reliable measure of upper limb capacity that is suitable for a wide range of patients including those with poor hand-related upper limb capacity.

Questionnaires. The subjects' impressions of the effectiveness of the intervention, the dose, and the ease of using the device/equipment will be captured with questionnaires including the Stroke Impact Scale Hand Section, the Neuro-QOL Upper Extremity Function Fine Motor ADL from the Patient Reported Outcomes Measurement Information System (PROMIS) Neuro-QOL Bank, and an end-of-treatment questionnaire. The purpose is to gain insight into how well the device and dosage are tolerated and the subjects' perception of effectiveness. The questionnaires will be administered at end of treatment by a staff member who will have no other interaction with the subjects.

Other Measures. Additional secondary measures include changes in muscle tone (modified Ashworth scale) and finger flexion and extension strength (dynamometry).These outcomes along with the

baseline characteristics collected and treatment adherence may provide insight into mechanisms of action and interpretation of the main findings.

Experimental Flow

Participation time for each subject will be ~9.5 months (inc. 3 months treatment, 6months follow-up). There are a total of 29 visits involved in this study.

Visit 1. Consent and eligibility (2 hrs)

Visit 2. Baseline Assessment (2 hrs)

Visit 3. Randomization, Device Setup and Training (2 hrs)

Visits 4-14. Therapy Visits (1.5 hrs)

Visit 15. Mid-Treatment Outcome Assessment (2 hrs)

Visits 16-26. Therapy Visits (1.5 hrs)

Visit 27. End of Treatment Outcome Assessment (2 hrs)

Visit 28. 3-mo post-Treatment Outcome Assessment (2 hrs)

Visit 29. 6-mo post-Treatment Outcome Assessment (2 hrs)

Selection Criteria

Inclusion Criteria

• Age 21 to 90 years old at time of randomization

• 6 to 24 months since a first clinical cortical or subcortical, ischemic or hemorrhagic stroke

• unilateral upper limb hemiparesis with finger extensor strength of ≤ grade 4/5 on the Medical Research Council (MRC) scale

• score of ≥1/14 and ≤ 11/14 on the hand section of the upper extremity Fugl-Meyer Assessment

• adequate active movement of shoulder and elbow to position the paretic hand in the workspace for table-top task practice

• able to follow 3-stage commands

• able to recall at least 2 of a list of 3 items after 30 minutes

• skin intact on hemiparetic arm

• surface electrical stimulation of the paretic finger and thumb extensors produces functional hand opening without pain (this will exclude patients who have too much flexor spasticity)
• able to hear and respond to cues from stimulator
• not receiving occupational therapy (no concomitant OT)
• full volitional hand opening/closing of contralateral hand
• demonstrates ability to follow instructions for putting on and operating the assigned stimulator or has caregiver to assist

Exclusion Criteria

• co-existing neurologic diagnosis of peripheral nerve injury, Parkinson's disease, spinal cord injury, traumatic brain injury, or multiple sclerosis
• uncontrolled seizure disorder, defined as having a seizure within the previous 3months
• brainstem stroke
• uncompensated hemi-neglect (extinguishing to double simultaneous stimulation)
• severe shoulder or hand pain, i.e., unable to position hand in the workspace without pain
• insensate to touch on forearm or hand
• history of potentially fatal cardiac arrhythmias with hemodynamic instability
• cardiac pacemaker or other implanted electronic system
• botulinum toxin injections to any upper extremity muscle within 3 months of enrolling
• pregnancy (unknown risks of surface NMES during pregnancy)
• lack of functional passive range of motion of the wrist or fingers of affected side
• diagnosis (apart from stroke) that substantially affects paretic arm and hand function
• deficits in communication that interfere with reasonable study participation
• lacking sufficient visual acuity to see the stimulator's display
• concurrent enrollment in another investigational study.

Potential Risks

Neuromuscular Electrical Stimulation Risks (pertain to CCFES and cNMES groups)

* Skin Irritation – When surface electrodes are used, it is possible that the subject will experience a temporary redness of the skin from either the electrodes, the conductive gel used with them, or any adhesive used to secure them. This risk is common. Skin irritation and redness from the electrical stimulation is also possible, but this possibility is rare and minimized by the type and intensity of stimulation that will be used. Participants will be instructed that redness should fade within an hour and that if redness persists, they should contact study staff. If necessary, electrodes or adhesives will be replaced with an alternative.

* Uncomfortable Sensation – Electrical stimulation of a muscle may be perceived as a twitching or vibrating sensation and may be uncomfortable. Electrical stimulation of a nerve may be perceived as a strong but short shock and may be uncomfortable. Electrical stimulation of the skin may be perceived as a "pins and needles" sensation and may be uncomfortable. Discomfort is common but stimulus parameters will be adjusted to the subject's comfort.

* Electrical Hazards – There is a possibility of an electrical shock hazard whenever electrical stimulation is used or whenever electrical equipment is used to make measurements. There is a possibility of an electrical burn whenever electrical stimulation with surface electrodes is used. The equipment to be used has been designed and tested to minimize these risks. Subjects will be trained how to use the stimulator safely and will be asked to adhere to a list of safety precautions. With these precautions, electrical hazards are rare.

* Stimulator Malfunction – There is a rare possibility that the stimulator may malfunction and produce painful stimulation after it has been programmed in the laboratory. The subject could feel a sudden burning sensation, which can damage the skin if it does not stop. The equipment to be used has been designed and tested to minimize this risk. If the subject experiences pain from the stimulation, they will be told to turn off the stimulator and/or unplug the electrode cables, stop using it, and contact study personnel.

* Unknown Effect of Stimulation on Pregnancy – The effect of electrical stimulation on a fetus is not known. If the subject is pregnant or is planning to become pregnant they may not participate in this

study. Subjects will be told to notify study personnel if they suspect that they become pregnant during the study.

All Groups

* Fatigue – During the treatment and assessment sessions, participants will practice several motor control tasks repeatedly or will be tested on how well they can move their arm and hand and perform specific tasks. These tasks involve concentration and repetition and may induce "mental fatigue" from the intensity of concentration required during these tasks or soreness from the repetition. Fatigue is common. Participants in previous similar studies have reported feeling very tired, needing to nap when they go home, or experiencing headaches following lab sessions. This is similar to what one might experience after working hard in a traditional occupational therapy session. Participants will be given rest breaks as needed during the treatment sessions. Additionally, participants will be encouraged to plan time to rest at home after their lab sessions until they know the effect the sessions will have on them.

* Breach of Confidentiality – When PHI is involved there is the rare risk of a privacy breach.

* Unknown Risks – There may be unknown or unforeseen risks associated with study participation.

Risk Management

If a subject experiences any of the risks described above, they will be asked to report it as soon as possible to the research team. Skin irritations, electrical burns, and electrical shocks will be assessed and treated by the study physiatrist if necessary. In the event of skin irritations associated with the electrodes, alternative electrodes may be used and/or the use of the stimulator may be temporarily suspended. In the event of uncomfortable sensations associated with the electrical stimulation, the stimulus parameters will be readjusted to the subjects' comfort. In the event of electrical burns, the subject will be retrained in the procedures necessary to guard against their occurrence. In the event of electrical shocks, the equipment will be assessed for faults. All equipment has been designed to

minimize the possibility of electrical hazards. To help prevent "mental fatigue", physical fatigue, pain and related issues, subjects will be provided with a five-minute rest break as needed during the lab session. Additionally, they will be advised to plan some time for rest or relaxation at home after lab sessions until they know the effect the increased concentration will have on them.

In addition to the risk management for the study described above, subjects in the CCFES and cNMES groups will be given a group-specific user's manual that describes how to use the stimulator safely. This will be reviewed with each subject before they are sent home with the stimulator. The manual will list the following safety precautions:

Safety Information

• IMPORTANT: Avoid handling the electrodes while the stimulator is on! Always remember to turn off the stimulator before you remove the electrodes.

• Always wash and dry the skin before applying the electrodes. Any mild soap is fine; avoid deodorant or perfumed soaps or lotions, as these affect skin adherence.

• Use new electrodes if the reused ones no longer stick well to the skin.

• Place electrodes on the skin only where instructed.

• Never position electrodes on the chest, across the heart, or on the neck.

• Do not place electrodes over broken skin as this may cause pain and skin irritation.

• Do not submerge the stimulator in water, or use around water (spills, bathtub/shower or sink).

• Do not operate dangerous machinery or drive while using the stimulator.

• Do not sleep while using the stimulator. Remain attentive during use to avoid skin burns.

• A slight reddening of the skin under the electrode is normal. This should fade after 1hour once the electrodes are removed. If you note redness or blistering beyond this, discontinue use and inform your therapist.

• The safety of electrical stimulation in pregnancy has not been determined; therefore, do not use the device if pregnant.

• Electrical stimulation should not be used by patients with implanted electronic devices(cardiac demand pacemakers etc.) unless under specialized medical supervision.

• Do not use the device if you have a history of potentially fatal cardiac arrhythmias.

• Electrical stimulation should not be used by people who have poorly controlled epilepsy.

• The stimulator has been programmed specifically for the intended user only. Do not allow anyone else to use the stimulator.

Statistical Analysis Plan

The primary analysis was based on a modified intention-to-treat (ITT) sample, which included participants in the group to which they were assigned who completed the treatment phase of the study. For all measures, changes from baseline were modeled using a linear mixed effects modeling approach, which accounts for missing values using maximum likelihood estimation. The linear mixed effects model using the restricted maximum likelihood (REML) estimator was employed, along with the Satterthwaite approximation to estimate the denominator degrees of freedom. While REML assumes normality of the random effects and residuals, it is generally more robust to violations of this assumption than traditional maximum likelihood, particularly in the estimation of fixed effects. The model included a random intercept to account for individual variability, and we specified a compound symmetry covariance structure to model the within-subject correlations. Least squares mean estimates were calculated after fitting each model for each group at each timepoint and were used to quantify within-group changes from baseline and between-group differences in change from baseline to 6 mos post-treatment. Statistical significance was set at $p<0.05$. No adjustments were made for multiple comparisons in order to maintain a balance between Type I and Type II error rates. This balanced approach to error control was prioritized rather than strictly minimizing Type I error at the expense of statistical power and increasing the risk of overlooking meaningful effects. Pair-wise Chi-square tests were used to compare responder rates between groups.

Exploratory subgroup analyses were performed using mixed effects models to test whether covariates (e.g., site, months since stroke, dose received, sex) moderated the change in BBT, UEFM, and ARAT scores across groups. A pre-planned analysis of only those participants with moderate hand weakness at baseline was conducted based on the prior study showing participants with moderate weakness achieved greater gains on the BBT than participants with severe hand weakness. Two pre-planned sensitivity analyses of the motor recovery outcomes were done. The first included all participants who were randomized to a treatment group regardless of the amount of treatment received. The second included only participants who received no other upper limb physical therapies during the treatment period and completed at least 80% of the planned treatment, i.e., at least 18 out of 22 FTP visits and at least 8 out of 10 home exercise sessions per week on average.