Contralaterally Controlled FES of Arm & Hand for Subacute Stroke Rehabilitation

NCT01688856

Study Protocol and Statistical Analysis Plan

Note: The text below was extracted from the IRB protocol for this study, which was first approved on June 22, 2012. The most recent amendment to the protocol was approved on:

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Study Protocol

Abstract

Impaired arm and hand function is one of the most disabling and most common consequences of stroke. Approximately 75% of the over 795,000 strokes that occur annually in the Unites States cause some degree of upper limb paralysis acutely. By 6 months post-stroke an estimated 65% of patients still cannot incorporate the impaired arm and hand into their daily activities, and nearly one third have chronic loss of upper limb function, which is often characterized by inability to extend the arm and open the hand. While the impact of upper limb impairments on disability and health is great, there are relatively few rehabilitation interventions designed to restore function to the impaired upper limb. Therefore, our long-term objective is to develop rehabilitation therapies for the paretic upper limb that are optimized for effectiveness, applicability, and implementation.

We have developed Contralaterally Controlled Functional Electrical Stimulation (CCFES), an innovative neuromuscular electrical stimulation (NMES) treatment for improving the recovery of hand function after stroke. Hand CCFES stimulates the paretic hand to open in proportion to the degree of volitional opening of the contralateral unimpaired hand. This enables the stroke survivor to perform active repetitive hand opening exercises, hand motor-control tasks, and functional tasks with the paretic hand. In this study, we add stimulation of elbow extensors controlled by the contralateral elbow in order to improve reach as well as hand opening. The purpose of this study is to maximize the treatment effect of CCFES by adding stimulated elbow extension. The specific aims are to (1) estimate the effect of Arm+Hand CCFES on upper limb motor impairment and activity limitation, (2) estimate the effect of adding stimulated elbow extension to Hand CCFES, and (3) define the relationship between treatment effect and time elapsed between stroke onset and start of treatment. Stroke survivors with upper limb hemiplegia (≤ 2 years) will be randomly assigned to receive 12 weeks of either Arm+Hand CCFES (stimulates elbow extension and hand opening), Hand CCFES (stimulates hand opening), or Arm+Hand Cyclic NMES (stimulates elbow extension and hand opening but with pre-set timing and intensity, i.e., not intention-driven), plus lab-based therapist-guided task practice. Upper limb impairment and activity limitation will be assessed at baseline, 6, 12, 20, 28, and 36

weeks.

This is the first randomized controlled trial of Arm+Hand CCFES in subacute upper extremity hemiplegia. Ultimately, the information learned in this study will serve to accelerate the development of a new treatment for reducing post-stroke disability.

Specific Aims

AIM 1: Estimate the effect of Arm+Hand CCFES on upper limb motor impairment and activity limitation.

Hypothesis 1: Stroke survivors treated with Arm+Hand CCFES have better outcomes on upper limb impairment and activity limitation measures than those treated with dose-matched Arm+Hand Cyclic NMES.

AIM 2: Estimate the effect of adding stimulated elbow extension to Hand CCFES.

Hypothesis 2: Stroke survivors treated with Arm+Hand CCFES will have greater reductions in upper limb impairment and activity limitation than those treated with Hand CCFES.

AIM 3: Describe the relationship between treatment effect and time elapsed between stroke onset and start of treatment.

Hypothesis 3: Patients who start Arm+Hand CCFES sooner after their stroke achieve better outcomes.

Methods and Procedures

The study includes three treatment groups: 1) Arm+Hand CCFES, 2) Hand CCFES, 3) Arm+Hand Cyclic NMES. The two CCFES groups will use a stimulator that activates the muscles of the paretic upper limb in response to and with an intensity proportional to movement of the contralateral arm and/or hand. This is in contrast to the Cyclic NMES, which delivers stimulation automatically and repeatedly with preprogrammed timing and intensity. For the Hand CCFES group, paretic finger and thumb extensors will be stimulated; for the Arm+Hand CCFES and Arm+Hand Cyclic NMES groups, both the elbow and hand extensors will be stimulated. The treatment dose will be equivalent for all

groups - approximately 2 hrs per day of self-administered stimulation-mediated exercise at home plus 70 min of functional task practice twice a week in the laboratory for 12 weeks.

Subjects will be assigned to one of the 3 treatments using an adaptive randomization algorithm to minimize group imbalances on: (1) time post-stroke (< 90 days vs. ≥ 90 days), (2) baseline motor status (moderate vs. severe), and (3) whether or not the pre-stroke dominant side is the paretic side. Patients with at least 10° active wrist extension, 10° active thumb abduction/extension, and 10° active extension in at least two additional digits will be considered to have "moderate" impairment, and patients with less movement than this who meet all the other motor criteria will be considered to have "severe" impairment.

All 3 groups will use a multi-channel surface stimulator. Stimulation will be delivered through standard 2"x2" square, 1.5"x3" rectangle, and 1.25" round self-adhering pre-gelled surface electrodes. The different sizes allow us to better target small and large muscles in the hand, forearm, and arm. The electrodes will be positioned on the hand, forearm, and arm of the impaired side in order to produce elbow extension in the Arm+Hand groups and hand opening in all groups without pain. For the CCFES groups, a command glove will be worn on the unimpaired hand and the stimulator will be programmed to stimulate hand opening in response to input from the command glove. The Arm+Hand CCFES group will wear an elbow cuff in addition to the command glove, and the stimulator will be programmed to stimulate elbow extension in response to input from the elbow cuff. The command glove and cuff will be instrumented with sensors (e.g., bend sensors) that interface with the stimulator. For the Cyclic NMES group, the stimulator will be programmed to deliver stimulation to the elbow and hand according to preprogrammed intensities and duty cycles. No command glove or elbow cuff will be used by the Cyclic NMES group.

The treating therapist will instruct and train all participants, and their caregivers if necessary, on how to put on the electrodes and use the stimulator at home according to their group assignment. Pictures of the electrodes correctly placed on the skin will be taken and given to the participants to guide them in electrode placement at home. A group-specific instruction manual will be reviewed with every participant, and will be given to them to take home. For participants in the Arm+Hand CCFES and

Arm+Hand Cyclic NMES groups, the treating therapist will make a home visit shortly after the setup and training visit (ideally, the day after) to set up a standard table and mobile arm supports that they will use during their self-administered home exercise.

The treatment period will be 13 weeks in duration, divided into two 6-week periods of actual treatment separated by 1 week to do mid-treatment assessments. Thus 12 weeks of actual treatment are provided over a 13 week period. Treatment consists of two components:

1) Therapist-guided task practice performed twice a week in the research laboratory. Subjects in the CCFES groups will use their assigned CCFES stimulation system to assist the paretic arm and/or hand in performing unilateral tasks. Subjects in the Cyclic NMES group will practice using their paretic arm and hand to perform unilateral tasks without stimulation. No stimulation will be used in the task practice sessions by the Cyclic NMES group because Cyclic NMES is not controlled by the subject and is therefore not conducive to performing tasks. To make up for the lack of stimulation during these sessions, the Cyclic NMES group will receive more stimulation than the CCFES groups during the home stimulation exercises so that all groups will receive an equivalent duration of stimulation every week. Each session will include 70 minutes of task practice. (These visits will not take place during week 7, the mid-treatment assessment week.)

2) Self-administered stimulation-mediated exercise performed 10 sessions per week at home. The Hand CCFES group will perform stimulated hand opening exercises while seated with both forearms supported by a table or by the armrests of their chair. The Arm+Hand CCFES group will perform stimulated reach-and-open exercises will sitting at a table with both forearms resting in mobile arm supports (to prevent shoulder fatigue). The Cyclic NMES group will also perform stimulated reach-and-open exercises, but with only the paretic forearm resting in a mobile arm support. Audio and LED cues from the stimulator will cue the CCFES subjects when to either open both hands (Hand CCFES) or reach forward with both arms and open both hands (Arm+Hand CCFES). Audio and LED cues will accompany the automatic stimulation for the Cyclic NMES group. For the two CCFES groups, each exercise session will last 46 minutes (two 23-min sets). For the Cyclic NMES group, each exercise session will last 60 minutes (two 30-min sets). All 3 groups will receive 10 hrs/week of stimulation in

total (taking into account the stimulation received during the lab sessions for the CCFES groups).

Compliance with home stimulation will be monitored with diaries and electronic data-logging. Every week, participants will be given a diary to log completion of exercise sessions. Also, the stimulator will log the date and time the unit is turned on and off and the date and time of start and completion of an exercise session. The diary will be collected weekly and compared with usage data from the stimulator in the presence of the participant at the beginning of each lab session.

Most subacute stroke patients have multiple rehabilitation needs that require intervention in addition to the study intervention. Therefore, to account for the potential confounding effect of concomitant therapies, the total number of hours of physical and occupational therapy sessions will be monitored during the entire study period. Any group imbalance in concomitant therapy will be adjusted for in the statistical analysis. The use of electrical stimulation or other experimental procedures involving the hemiparetic upper limb, changes in spasticity medication, Botulinum toxin injections to upper limb muscles, intrathecal baclofen, use of an arm sling, and use of a resting hand splint will be discouraged unless they are absolutely necessary.

All subjects will undergo assessments of upper limb impairment and activity limitation by a blinded assessor prior to treatment and at 6, 12, 20, 28, and 36 weeks. The assessments will be completed in two separate sessions (less than 7 days apart) lasting < 2 hrs each in order to avoid possible fatigue effects. Participants will receive an incentive payment of $25 when they complete each set of follow-up assessments (i.e., at 20, 28, and 36 weeks for a total of $75 per participant).

Outcome Measures

All subjects will undergo assessments of upper extremity impairment and activity limitation by a blinded assessor prior to treatment and at 6, 12, 20, 28, and 36 weeks (unless otherwise specified below). In addition, at the 12-week assessment a questionnaire will be given regarding device usability, treatment dosage, and treatment effectiveness. The assessments will be completed in two separate sessions (less than 7 days apart) lasting < 2 hrs each in order to avoid possible fatigue

effects. The outcome measures and procedures are:

1) Box and Block Test (primary). The Box and Block test is a measure of gross 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 a one-minute period.

2) Reaching Workspace. Subjects will be seated with their trunk restrained using a harness with straps going over both shoulders. A padded plastic forearm-wrist orthosis will be used to attach the subjects' arm to a gimbal on the end of the armature of a HapticMaster robot. The HapticMaster has a negligible amount of inertia during a reaching task and will measure the reaching workspace of the subject as he/she traces out as large a reaching area as possible (following Sukal, Exp Brain Res, 2007). The HapticMaster will be used to provide a frictionless haptic surface (i.e., a "haptic table") to simulate a table so that the reaching table workspace can be measured as well as the reaching workspace when the arm is unsupported. Reaching workspace will be measured under 4 conditions: 1) with the hand at rest and the arm fully supported, 2) with the hand at rest and the arm unsupported, 3) during attempts to volitionally open the hand with the arm fully supported, 4) during attempts to volitionally open the hand with the arm unsupported.

3) Fugl-Meyer Motor Assessment (upper extremity portion). The Fugl-Meyer Motor Assessment (FMA) is a valid and reliable measure of post-stroke motor impairment. An assessor requests the subject to attempt specific volitional movements of the upper limb (shoulder, elbow, forearm, wrist, and hand), and rates their ability to perform each movement on a 3-point ordinal scale (0, cannot perform; 1, perform partially; and 2, perform fully). The maximum score is 66 (upper limb portion).

4) Stroke Upper Limb Capacity Scale (SULCS). This test will be administered when the outcome assessments are done. 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. The SULCS takes approximately 10-15 minutes to complete.

5) Arm Motor Abilities Test. The ability of a hemiparetic upper limb to execute specific ADL tasks will be assessed with the Arm Motor Abilities Test (AMAT). In contrast to global measures of activity limitation, the AMAT assesses upper limb specific tasks and does not allow for compensation with the unimpaired side. The AMAT consists of 17 compound tasks composed of 1 to 3 component tasks performed continuously without the subject's awareness of how the components are defined or scored. Unilateral activities are performed with the affected upper limb. Bilateral tasks are performed using (or attempting to use) the dominant extremities in the same roles as prior to onset of the stroke.

6) Motor Activity Log (MAL). The MAL is a 30-item structured interview that assesses the subject-reported use of the hemiparetic arm outside the treatment setting. In the interview the subjects are asked to rate how well (Quality of Movement) and how much (Amount of Use) they used their impaired arm and hand to accomplish each of 30 ADL in the past week. The subjects may select responses between 0 = never used and 5 = same as pre-stroke. The interview will be administered prior to the assessments of motor impairment and activity limitation at baseline, 12 weeks, and 36 weeks.

7) Questionnaire. A questionnaire will be administered to assess the participants' impression of the intervention's dose and ease of using the device. The purpose is to gain insight into how well the device and dosage are tolerated and what changes to make in future studies. In addition, the questionnaire will ask the subject to rate their ability to reach and open their hand and to use their hand to perform tasks at home and whether they think the treatment had any effect on their arm and hand function.

Experimental Flow

In this RCT, stroke patients who are within 2 years of stroke onset and have upper limb hemiplegia will be randomized to one of 3 groups: (1) Arm+Hand CCFES, (2) Hand CCFES, or (3) Arm+Hand Cyclic NMES. Treatment for all 3 groups will last 12 weeks (two 6-week blocks separated by a week during which mid-treatment assessments occur). Blinded assessment of upper limb impairment and activity limitation will be made at baseline, 6, 12, 20, 28, and 36 weeks. Although treatment is defined

as lasting 12 weeks, the 6-week (mid-treatment) assessments will take place during their own week, resulting in an overall Treatment Period of 13 weeks: 6 weeks of treatment with home stimulation + lab therapy sessions, a week during which the mid-treatment assessments take place, and 6 more weeks of treatment with home stimulation + lab therapy sessions. During the mid-treatment assessment week, subjects may still undergo home stimulation exercise, with the limitation that they not do so during the 24-hour period preceding a lab assessment visit.

There are a total of 40 visits involved in this study; 2 are home visits, 38 are visits to the lab.
Visit 1. Consent and eligibility (2 hrs)
Visit 2. Baseline Assessment 1 (2 hrs)
Visit 3. Baseline Assessment 2 (2 hrs)
Visit 4. Randomization, Device Setup and Training (2.5 hrs)
Visit 5. Home equipment setup (2 hrs)

The treatment period for all 3 groups will be 13 weeks in duration (12 weeks of defined treatment + mid-treatment assessments during week 7), with the defined treatment consisting of two components:

1) Therapist-guided task practice performed twice a week (70-min each) in the research laboratory.
2) Self-administered stimulation-mediated exercise performed 10 sessions (46-60 min each) per week at home. Also, all participants will be encouraged to use their affected hand to perform tasks at home as much as possible in order to overcome “learned non-use” by creating a habit of using the affected hand."

Visits 6-17. Therapist-Guided Task Practice. (Treatment: Weeks 1-6)
Visit 18. 6-Week Outcome Assessment 1 (Mid-treatment: Assessment week 7)
Visit 19. 6-Week Outcome Assessment 2 (Mid-treatment: Assessment week 7)
Visits 20-31. Therapist-Guided Task Practice. (Treatment: Weeks 8-13)
Visit 32. Home equipment pickup (30 min)
Visit 33. 12-Week Outcome Assessment 1 (End of treatment: Week 14)
Visit 34. 12-Week Outcome Assessment 2 (End of treatment: Week 14)

Visit 35. 20-Week Outcome Assessment 1 (2 months post-treatment)

Visit 36. 20-Week Outcome Assessment 2 (2 months post-treatment)

Visit 37. 28-Week Outcome Assessment 1 (4 months post-treatment)

Visit 38. 28-Week Outcome Assessment 2 (4 months post-treatment)

Visit 39. 36-Week Outcome Assessment 1 (6 months post-treatment)

Visit 40. 36-Week Outcome Assessment 2 (6 months post-treatment)

Selection Criteria

Inclusion Criteria

• Age ≥ 21 and ≤ 80

• ≤ 2 years of first clinical hemorrhagic or nonhemorrhagic stroke

• Skin intact on hemiparetic arm and hand

• Able to follow 3-stage commands

• Able to recall 2 of 3 items after 30 minutes

• Medically stable

• MRC ≤ 4 for finger extensors on paretic side

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

• Caregiver available to assist with device daily – OR – able to independently don elbow cuff on unaffected arm

• Full volitional elbow extension/flexion and hand opening/closing of unaffected limb

• Upper extremity hand section of FMA ≥ 1 AND ≤ 11/14

• Unable to simultaneously fully extend the elbow and fully open the hand toward tabletop object with arm unsupported (i.e. cannot voluntarily achieve the maximum PROM available)

• Functional PROM (minimal resistance) at shoulder, elbow, wrist, and hand simultaneously on affected side (i.e., there exists enough PROM to reach and acquire table-top objects).

• Able to hear and respond to stimulator cues

• While relaxed, surface NMES of finger extensors and thumb extensors and/or abductors produces a functional degree of hand opening without pain.

• While relaxed with the forearm supported with a mobile arm support, surface NMES of elbow extensors (triceps) produces functional elbow extension without pain.

• Patient must be able to sit unassisted in an armless straight-back chair for the duration of the screening portion of the eligibility assessment.

Exclusion Criteria

• Co-existing neurological condition other than prior stroke involving the hemiparetic upper limb (e.g., peripheral nerve injury, PD, SCI, TBI, MS).

• Severely impaired cognition and communication

• Uncontrolled seizure disorder

• History of cardiac arrhythmias with hemodynamic instability

• Cardiac pacemaker or other implanted electronic device

• Pregnant

• IM Botox injections in any UE muscle in the last 3 months

• Insensate arm, forearm, or hand

• Uncompensated hemi-neglect (extinguishing to double simultaneous stimulation)

• Severe shoulder or hand pain

• Severe depression on Beck Depression Inventory (>=13 on BDI-fast screen)

Potential Risks

Surface Electrode Skin Irritation – When surface electrodes are used, it is possible to experience a temporary redness of the skin from either the electrodes or the gel and adhesive used to secure them. If this occurs, the electrodes will be replaced with an alternative. Skin irritation and redness from the electrical stimulation is also possible, but this possibility is minimized by the type and intensity of stimulation that will be used. Irritation from the electrodes is common, occurring in > 10% of subjects.

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. Stimulus parameters will be adjusted to the subject’s comfort. Discomfort associated with electrical stimulation is common, occurring in > 10% of subjects if the stimulus parameters are not well-adjusted.

Vasovagal Reaction: "Feeling faint" is a possible response to feeling electrical stimulation for the first time. The vasovagal response is characterized by reduced heart rate and decrease in blood pressure, and it can be accompanied by loss of consciousness. The response can also be accompanied by dizziness, faintness, sweating and turning pale. This reaction is uncommon, occurring in less than 5% of subjects during the first exposure to electrical stimulation.

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 even after it has been properly programmed in the laboratory. The sensation may be a sudden burning sensation, which can damage the skin if it does not stop. If you experience pain from the stimulation, you should turn off the stimulator and/or unplug the electrode cables, discontinue its use, and contact study personnel.

Fatigue or Pain: There is a possibility that the concentration and repetition associated with activities during lab sessions may cause "mental fatigue" from the intensity of concentration required during these tasks, or physical fatigue or pain (for example, muscle ache or shoulder pain) due to the repetitive tasks. This will vary from person to person. Some past participants have reported feeling very tired, needing to nap when they go home, or experiencing headaches following lab sessions. This is similar to what might be experienced after working hard in a traditional occupational therapy

session.

Arm Shaking by the Robot: During tests of the subject's ability to reach, the arm will be attached to a robot arm. The arm of the robot can move up and down and in and out, and may have small oscillations under some conditions which would be perceived as shaking the subject's arm. The settings on the robot will be set to minimize the chances and the amount of oscillations. If the robot does start to oscillate, there is a large button that the subject or the investigator can press to immediately turn the robot off.

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 minimize the risk of vasovagal response to stimulation, research personnel will tell the participant what sensation to expect from the stimulation and will turn up the stimulation very slowly, allowing the subject to get used to it. 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 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 use the stimulator on their own. The manual will list the following safety

precautions:

• 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. Generally 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 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 1 hour once the electrodes are removed. If you note redness or blistering beyond this, discontinue use and inform study personnel.

• The safety of electrical stimulation in pregnancy has not been determined; therefore, we do not enroll pregnant women.

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

• Do not participate in this study 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.

For the assessments involving the subject's arm being attached to a robot arm, the settings on the robot will be set to minimize the chances and the amount of oscillations. If the robot does start to oscillate, there is a large button that the subject or the investigator can press to immediately turn the robot off.

Statistical Analysis Plan

We hypothesized that participants treated with A+H CCFES would have greater improvements in upper extremity motor function from baseline to 6-months post-treatment than participants treated with Hand CCFES or A+H cNMES. The distributions of baseline characteristics were compared in the three groups by nonparametric Kruskal-Wallis tests or Fisher's Exact tests, as appropriate, with a significance level of 0.05. For each outcome measure, we used a mixed effects modeling approach evaluating fixed effects for group, time and group by time interaction and a random intercept and slope. Least square (LS) means, calculated using model estimates and adjusted for missing values, were computed for each group at each time point. We used differences of LS means from baseline to 6 months post-treatment to estimate the within-group mean changes and between-group differences in change. We calculated 95% confidence intervals (CIs) for these point estimates; standard errors for LS means are adjusted for model covariance parameters. CIs that do not contain zero were considered to be indicative of significant changes. Effect size (Cohen *d*) estimates were calculated as the between-group difference in outcome variable mean divided by the common standard deviation of the outcome variable. Secondarily, we hypothesized that participants who were <90 days post-stroke or had moderate hand impairment at baseline would improve more than subjects who were >90 days post-stroke or had severe hand impairment at baseline. We used a similar mixed effects modeling approach with analysis of LS means to test these secondary hypotheses for each outcome across all participants and within each group.