COVER PAGE

PROTOCOL TITLE:

Novel training environment to normalize altered finger force direction post stroke

PRINCIPAL INVESTIGATOR:

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Trial registration:

Clinicaltrials.gov NCT03995069

1.0 Objectives / Specific Aims

The objective of this project is to determine if 3D finger force training is an effective tool in restoring hand function post stroke.

Aim 1: Determine the effect of 3D finger force training on behavioral hand function

Hypothesis: Hand function will improve more in the experimental group than the control group.

Aim 2: Determine the effect of 3D finger force training on finger force direction control

Hypothesis: The experimental group will achieve greater ability to direct finger force than control after the training.

Aim 3: Determine the biomechanical mechanisms underlying improvement in force direction control

Hypothesis: The training results in improved muscular coordination.

2.0 Background

Our hands constitute our primary means of interacting with the external world. They allow us to dexterously manipulate objects such as tools, dishes, and smart phones. This exquisite manipulation requires precise generation of forces at the finger and thumb tips. Unfortunately, control of these forces can be profoundly impaired following stroke, thereby resulting in the object being mishandled, or not handled at all, and failure at task execution. Thus, hand function and use and utility of the entire upper extremity can be dramatically diminished, with ramifications for self-care, work, and leisure.

Both finger movement[1,2] and force control[3] are impaired after stroke. The central nervous system uses two separate neural strategies to control digit force generation vs. movement.[4] Therefore, both neural strategies must be independently rehabilitated to achieve proper hand function. Clinical motor learning literature suggests that the best treatment modality involves training in volitional movements with explicit feedback. Current therapy focuses on training of volitional movement with explicit feedback.[5] Unfortunately, digit force control is rarely explicitly addressed in therapy.

This gap in treatment is due to a lack of tools to provide explicit feedback on patients' volitional finger force generation. To address this unmet need, we developed a novel tool for practice of volitional three-dimensional (3D) force generation with explicit feedback.

3.0 Intervention to be studied: 3D finger force training (Fig 1)

Subjects will place their fingers into thimbles that are firmly attachable to the grip surfaces that are attached to force sensors (Fig 1).

Subjects in the experimental group will practice generating their finger force in various directions in 3D. Subjects will receive explicit visual feedback on force magnitudes in 3D in the computer screen (Fig 1).

The control group will practice 1D force generation with no explicit feedback on the non-target direction force, thus no feedback on directional control of force. This control condition is more accessible in clinic and cheaper, but does not provide explicit feedback for digit force direction that

is essential for successful object manipulation based on our preliminary data. This experimental vs. control comparison will determine the therapeutic value of the 3D force feedback vs. 1D.

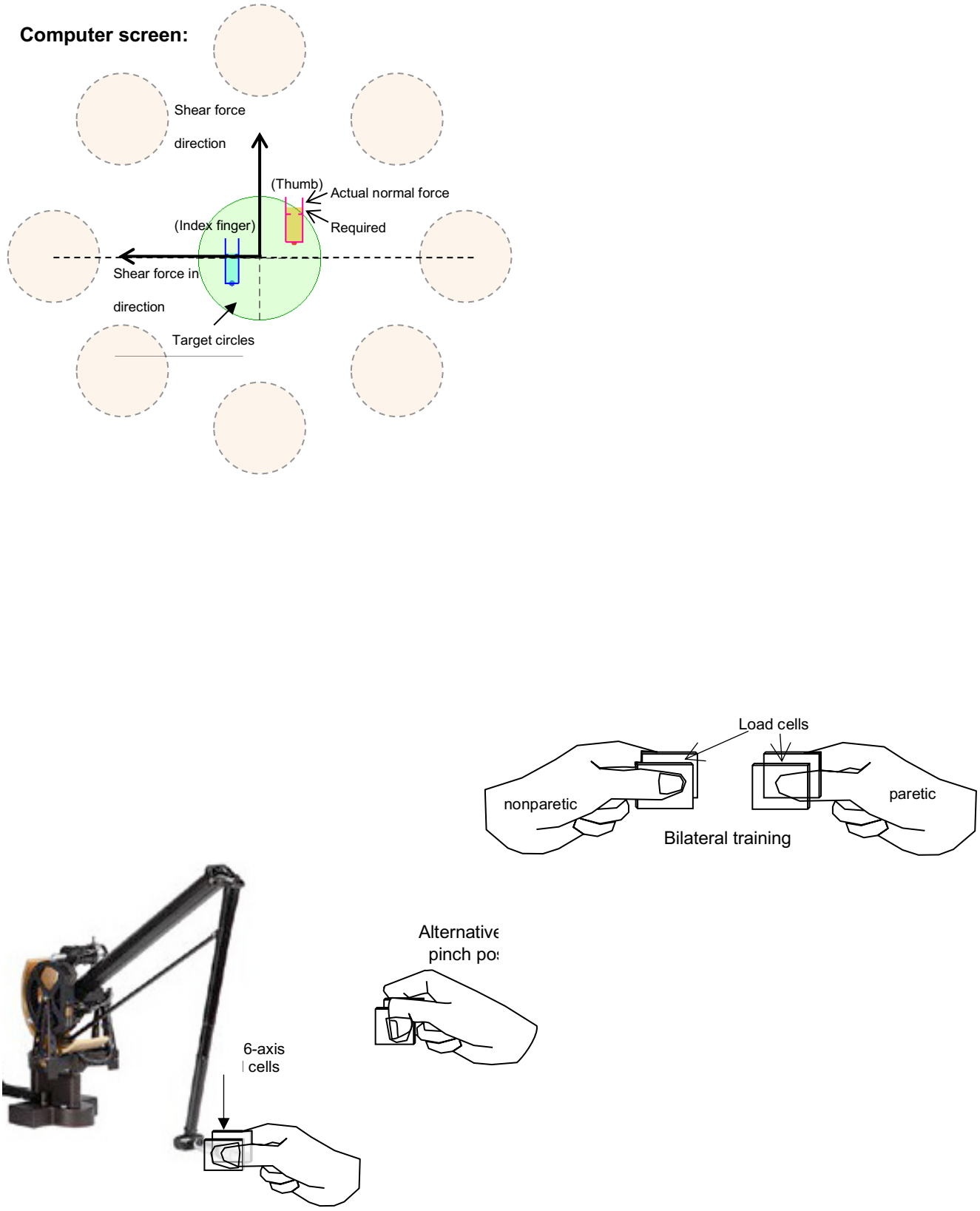

Figure 1. Finger force training setup

Training will progress by varying posture requirements (toward forearm pronation, elbow extension, shoulder flexion,[6] and whole body from seated to standing to walking[7]) and increasing finger force level,[8] introducing feedback delay (to solicit increased reliance on intrinsic sensory feedback processing), and incorporating unilateral/bilateral training for both groups. External arm support may initially be provided (Fig 2A) but the extent of arm support will be reduced as the subject progresses. The whole body posture will progress from sitting to standing to walking with a harness for safety (Fig 2B), only if the participants can stand or walk without support. Regardless of the whole body posture, the training will be the finger force control (Fig 1).

(A) (B)

Figure 2. Arm support (A) and harness (B)

There is no FDA approval on this finger force control training. The finger force training does not apply any energy to the subjects. The training setup measures subjects' voluntary finger force generation and provides visual feedback to the subjects on a computer screen (Fig 1).

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

- Age: 18 years old or older
- Survived a stroke at least 3 months ago
- Moderate to severe hand impairment (Chedoke-McMaster Hand Stage 2-4)
- Ability to generate palpable volitional grip force upon cue
- Sufficient cognitive ability to participate (NIH Stroke Scale, NIHSS, Questions and Commands score = 0-1)
- Ability to recognize all quadrants of the visual field (NIHSS Visual Field Test score = 0)

Exclusion Criteria

- Concurrent upper limb rehabilitation
- Inability to follow 2-step commands

- Severe muscle tone prohibiting passive movement of the fingers or proper placement of the fingers on the force sensors as needed to participate in the training (Modified Ashworth Scale, MAS=4-5 out of 5)
- Change in spasticity medication or botulinum toxin injection in the upper limb within 3 months prior to or during enrollment
- Total sensory loss on fingertips (NIHSS Sensory score=2)
- Comorbidity (e.g., orthopaedic conditions that limit ranges of motion, premorbid neurologic conditions)
- Language barrier or cognitive impairment that precludes providing consent

- **Screening**: Eligibility will be determined based on the potential participant's verbal disclosure or standardized clinical assessments. To minimize travel and face-to-face contact, video screening may also be used using HIPAA-compliant video applications (e.g., Microsoft Teams).
- **Sex/race/ethnicity**: We will include stroke survivors of all genders and all racial and/or ethnic groups that are representative of the demographics of Americans who had a stroke. We will not exclude people based on sex/gender, racial or ethnic group. We will aim to construct a participant pool that matches post-stroke survivor distributions in South Carolina. Our target enrollment for sex and race/ethnicity based on the demographic data and stroke surveillance data in South Carolina. This recruitment is possible, because we perform outreach to recruit stroke survivors of all sex, racial, and ethnic groups, as shown by our stroke registries currently having 48% female and 43% ethnic/racial minorities.
- **Children**: Children under the age of 18 years will be excluded. The rationale for exclusion of children is that stroke predominantly occurs in adults, and stroke is very rare in children. Importantly, these rare cases may actually differ in their etiology from the participants we propose to study.

6.0 Number of Subjects

A total of 60 subjects will be recruited.

7.0 Setting

All human subject involvement will take place at Ralph H. Johnson VA Medical Center.

8.0 Recruitment Methods

- We will get referrals from the VA Charleston Neuro Clinic. We will enroll participants upon discharge from usual-care therapy. The VA Charleston Neuro Clinic treats >300 new stroke cases every year.
- The IRB-approved VA stroke registry (IRB# 43107 "VA Stroke Rehabilitation Research Database") has contact and demographic information for 497 post-stroke Veterans who were seen at the Ralph H. Johnson VA Medical Center and are interested in participating in research. We will recruit from the VA stroke registry.

- A dedicated recruiter visits local clinics and performs community outreach to enroll patients into the RESTORE stroke registry supported by the NIH COBRE-funded Stroke Recovery Research Center (Pro#00037803). We will recruit from RESTORE.
- A chart review will be conducted for research purposes. Potentially eligible patients will be identified. We will submit a Research Data Request to obtain a recruitment report of MUSC patients who potentially meet eligibility criteria. The potentially eligible patients who have agreed to be contacted for future research by logging their MUSC Research Permissions preferences in MyChart will be contacted by phone, letter, or email and invited to participate. Other patients who did not update their MUSC Research Permissions in MyChart may also be cold-contacted by phone, letter, or email to be informed of the study if it is appropriate. We will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment.
- Similarly, potentially eligible patients in the VA medical records will be contacted by phone, letter, or email.
- In addition, advertisement via internet (e.g., South Carolina Research Studies Directory) will be used.

9.0 Consent Process

The consent process will take place in a private room when the potential participant comes to the laboratory on a scheduled time agreed upon between the study personnel and the participant. The content of the consent will be verbally explained to the participant and the participant will be asked to raise any questions and concerns. If the person requests a waiting period, then one will be given. If the person desires to consent immediately, then the person will provide consent immediately.

10.0 Study Design / Methods

- **Study design**: The study will be a randomized controlled trial. Subjects will be randomly assigned to either the experimental or control group using block randomization to ensure balance (half in the experimental, half in the control). Block sizes will be random (4, 6, or 8). The block randomization will be stratified equally by the moderate vs. severe impairment level (with the Fugl-Meyer Upper Extremity assessment cut-off score of 19[9]).
- **Intervention schedule**: All subjects will undergo approximately two-hour force training, 3 times per week for 6 weeks. The experimental group will practice for various target force direction to explore the 3D force workspace and receive explicit feedback in 3D force, while the control group will receive feedback in 1D on a computer screen (in target direction only with no explicit feedback on other directions, thus no training in force directional control, much like simple squeeze ball repetitions). The training dose will be controlled by having a minimum of 8 sets with 14 targets each (a total of 112 targets) per session, with maximum 30 sec allowed for each target (up to 56 min/session).
- **Evaluations**: Outcome measures will be assessed at baseline, immediately after 2 and 4 weeks of force training, at post (within a week after 6-wk force training), and 1 month after training ends (i.e. follow-up to assess retention). The baseline measurement will take place 3 times over 3 weeks prior to training to examine the baseline recovery rate. Each evaluation visit will take 1-5 hours. Evaluation for each outcome is detailed below.

- Behavioral hand function: Subjects' upper extremity function will be assessed using conventional clinical assessments used in occupational/physical therapy in which participants will be asked to move the affected hand and arm, grasp objects and perform prescribed tasks (e.g., lifting an object off the table, releasing the object into a bin, gripping hard, reaching as high or far as possible, opening the hand as much as possible). These tests will be videotaped for scoring. The joint positions and muscle activity during these tasks will also be recorded. The behavioral hand function assessments will last approximately 1 hr.
- Interview: Subjects will be interviewed after the completion of the intervention in a semi-structured interview format, to discuss the impact of the training on their day-to-day life. The interview will be audio-recorded. The interview will last approximately 30 min.

12.0 Data Management

- Recruitment projects are housed in REDCap. Only study personnel will have access to the REDCap database while actively enrolling for the study.
- Power analysis: The study was designed primarily to power the analysis of digit force direction. For the primary power analysis, based on previous studies, a clinically meaningful difference in force direction was deemed to be 6º. Reduction of force deviation to a value below <20º is expected to result in increased ability to manipulate objects.[10] The mean force deviation for stroke survivors in Chedoke Hand Stage 2-4 is anticipated to be 25.6º based on our preliminary data.[10] Therefore, a 6º change in force direction is expected to lead to a substantial functional improvement.

  Our study is longitudinal with 4 primary time points. In the analyses, an autoregressive (AR(1)) covariance structure will be considered for the within-subject correlations (while other structures will also be examined). For a standard deviation of 6.6º (based on the force direction data in our preliminary study), an alpha level of 0.05, 90% power, and the AR(1) correlation between observations on the same subject of 0.8 (based on the preliminary study), a sample size of 22 participants per group will be adequate to detect a difference of 6º. Adjusting for an expected attrition rate of 15% and screen failure rate of 12%, a sample of 30 per group (for a total of n=60) is planned.
- Analysis: The primary formal analysis for the primary outcome measure will be a repeated measures general linear model with an AR(1) structure (although other structures will be considered and compared). The primary independent variables are group (experimental vs. control), evaluation time (baseline (3rd), 2, 4, and 6 weeks for the primary analyses; all 3 baselines and follow-up will be included in subsequent analyses), and their interaction (group× evaluation time). In addition, we will include sex as an independent variable along with its interactions to study gender differences. If the group×evaluation time interaction is significant, then the main alternative hypothesis of interest, that at 6 weeks there is difference between the two groups, will be tested using post-hoc tests. Greater improvement for the experimental than control group will support the hypothesis.

  The time course of the effect will also be examined over the 6-week training period and at follow-up. As digit force direction will be recorded throughout the training sessions, spaghetti plots will be generated over the 18 training sessions along with evaluation sessions to examine a more detailed time course. Also in secondary analysis, other covariates such as initial impairment levels will be included. If missing data arise, multiple imputation methods will be applied under the assumption of missing at random (MAR).

The same analysis approach will be applied to each secondary outcome measure. Bonferroni correction will be applied to adjust for multiple comparisons. Data reduction methods may also be considered.

- Qualitative Analysis: Interviews will be audio recorded and transcribed verbatim. Qualitative data will be analyzed using the popular constructivist grounded theory methodology.[11,12] The 'Framework Analysis' commonly used in applied qualitative research will guide the data analysis process[13] and includes five key stages: familiarization, identifying a thematic framework, indexing, charting, mapping, and interpretation.[14,15] Two researchers will conduct a high-level reading of transcripts to consolidate the data into analyzable units.[14] Text segments ranging from a phrase to several sentences may be assigned codes a priori (e.g., areas of significance to this project). Additional codes will be created to capture new themes emerging from the data. Two researchers will independently read approximately 25% of the transcripts to establish inter-rater reliability for the final coding hierarchy that will be applied to analyze the all data. Disagreements in definitions or assignment of codes will be resolved through group discussion and further review of the data to achieve consensus. A thematic codebook will be created to document the final codes. Qualitative memos will be used throughout the analysis to document reflective notes, concepts and themes. Transcripts will be carefully read and coded with the assistance of qualitative data management software, constantly comparing the results against the original text for rigor.[16] From final coded transcripts, text segments will be analyzed using a computational process of queries and comparisons.
- Confidentiality: All data except for the consent forms and HIPPA forms will be coded at the time of data recording such that personally identifiable information is not used in the data recording. Qualitative interviews will not have identifiable information such as participant names. Videos of the behavioral hand function will be recorded such that the hand, arm, and object being grasped will be in the video but not the participant face. All electronic data will be stored in a password-protected research server that is accessible to study personnel only. The server is backed up every day and maintained 24/7 by IT specialists. All paper data with personally identifiable information including the consent forms and HIPPA forms will be stored in a key-locked cabinet in a key-locked room that is accessible to study personnel only. Other paper data without personally identifiable information including testing sheets documenting testing sequences and notes will also be stored in a cabinet in a key-locked room that is accessible to study personnel only.
- Data sharing: Data will be shared with collaborating sites, Medical University of South Carolina (MUSC) and the VA Centralized Transcription Services Program. De-identified data will be shared with another collaborating site, North Carolina State University (NCSU). De-identified coded data will be reported and/or shared with the public and other investigators in publications, in ClinicalTrials.gov, or via network storage.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

- The proposed research is a single-site randomized controlled clinical trial. A Data Safety Monitoring Board (DSMB) will be used. The primary purpose of the DSMB is to ensure the safety of participants and the validity and integrity of data collected during the study. The overall framework involves biannual review of the enrollment/retention, safety and adverse event data, and quality control data by the DSMB during the tenure of the proposed research.

- DSMB composition: The DSMB will be composed of three professionals with expertise related to the proposed area of study who are not involved with the study design or experiments. Specifically, the DSMB will include: (1) a board-certified stroke neurologist who also is a stroke recovery researcher and is experienced in care of chronic stroke survivors and their recovery; (2) a registered and licensed occupational therapist who also is a quantitative researcher in outcomes measurement and research design; and (3) a biostatistician with expertise in design and analysis of clinical trials. This multidisciplinary group has experience with management and monitoring of clinical intervention trials involving individuals following stroke, and brings substantial expertise adequate to serve as the DSMB.
- DSMB responsibilities:
  - Prior to any enrollment, the DSMB will review the study design, protocol, informed consent documents, amendments, recruitment/enrollment plan, statistical analysis plan, and data and safety monitoring plan, and document the agreement or recommendation.
  - Once the enrollment begins, the DSMB will convene every 6 months to review the progress of the trial.
  - The DSMB will review the enrollment/retention data including new enrollments, progression of the enrollees' participation in the study, any discontinuation of participation in the study with or without adverse events, and the current enrollment status compared to the project time line.
  - The DSMB will review data quality and quality control data.
  - The DSMB will review safety and adverse event data. The DSMB will review the aggregated summary data as well as the individual participants' data (coded). The DSMB will discuss participant risk vs. benefit and other factors that may potentially affect study outcomes. The DSMB will make recommendations for appropriate action to maintain a reasonable safety profile for the study.
  - The DSMB will ensure that all serious adverse events have been followed to resolution, and that the appropriate agencies (including the IRB and/or federal funding agency) have been informed.
  - The DSMB will advise the IRB and the study investigators as to whether the protocol should continue as scheduled or undergo any modification due to findings from the monitoring process. The DSMB may recommend stopping the study early if the study has unanticipated safety concerns that warrant stopping.
  - The DSMB will review study performance as well as make recommendations and assist in resolution of problems reported by the PI.
  - The DSMB will ensure the confidentiality of the study data and the results of monitoring.
  - The DSMB will document their reviews in writing and provide a report to the IRB to summarize oversight activities, recommendations and any concerns regarding participant safety. The report will include participant characteristics (including distributions across race and sex), retention and disposition of study participants, quality assurance issues and reports of adverse events, significant/unexpected adverse events and serious adverse events.
  - The DSMB will review final analysis results upon completion of the data collection.
- Reporting of safety data: All serious adverse events will be reported to the IRB as they occur. All enrollment/retention data, and safety and adverse event data will be reported to the DSMB during the review. The DSMB will review the data and submit a report to the IRB. Summative safety data will be reported to VA Research Services, ClinicalTrials.gov, and in publications. As such, we will register this study in ClinicalTrials.gov as soon as the study commences and report results including all adverse events as soon as the study is completed following the guidelines. To protect participants' confidentiality, personally

identifiable information will not be used for reporting. Only de-identified or aggregated data will be used for reporting.

14.0 Withdrawal of Subjects

- Subjects who do not show up on scheduled visits or do not complete the intervention in 10 weeks may be withdrawn by the investigator. Subjects who are or become medically unstable may be withdrawn by the investigator.
- For those who withdraw from the research, their data collected up to that point may be used by the investigator.

15.0 Risks to Subjects

There is a slight risk for loss of confidentiality although researchers will take appropriate steps to protect any information collected about the participants. There is a minor risk of physical and mental fatigue from engaging in the study activity. There is a minor risk of discomfort from having muscle activity sensors or joint position sensors during hand movement during the behavioral hand function assessment. There is a minor risk of skin irritation from adhesives used to affix muscle activity sensors or joint position sensors during the behavioral hand function assessment. There is a risk of fall from standing or walking, although subjects will be wearing a whole body harness to prevent such events. The treatment one person receives may prove to be less effective or to have more side effects than the other study treatment. The experimental treatments may have unknown side effects.

16.0 Potential Benefits to Subjects or Others

There may be no benefit from participating in this study. The potential benefit is that the training the participant receives may help recover their hand function, although this cannot be guaranteed. The knowledge regarding the merit of force training is important to create a new therapy option for people who had a stroke and may benefit stroke survivors in general. The risks are deemed reasonable in relation to the potential gain of knowledge regarding the effect of novel force training in enhancing hand force control and hand function after stroke.

17.0 Sharing of Results with Subjects

If the subject agrees, the data collected and generated from this study will be shared to the Registry for Stroke Recovery (RESTORE-Pro#00037803) by the subject's registry ID. Sharing data from this study with the registry will allow for more targeted recruitment efforts in the future and allow researchers at MUSC to have a more complete registry with key stroke recovery elements including common data and physical function characteristics that are applicable to multiple studies. MUSC researchers and collaborating facilities will be able to query data sets to learn more about recovery of subjects after their stroke through institutionally managed secure servers that will assure HIPAA privacy and security compliance.

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