NCT04112173

Fall-recovery training for those with chronic stroke and low falls self-efficacy

Study Protocol and Statistical Analysis Plan

9/18/2019

1. Protection of Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

This feasibility study has a single-arm, repeated measures design in which a non-active control period is followed by an intervention period. In other words, there are three assessment visits (baseline, assessment after non-active control period, and assessment after experimental intervention).

A total of five participants with chronic stroke (i.e. 6 or more months after stroke) are expected to qualify for this study. All participants must have low balance self-efficacy, as determined by an Activities-Specific Balance Scale (ABC) score less than 68. We plan to enroll an additional two participants, anticipating that these participants will not be eligible to continue in the study after the initial DXA and physical therapist screening.

All in-person activities will occur at the University of Delaware.

b. Study Procedures, Material, and Potential Risks

Proposed involvement of human subjects will include the following:

1. Study participation requires nine laboratory visits. Assessment visits will take up to four hours. Training visits will take one to two hours.
2. Upon enrollment, the Fugl-Meyer Lower Extremity assessment and the Stroke Impact Scale will be administered to characterize participant impairment.
3. We will record the height, mass, and age of all participants.
4. Study staff will provide an initial screening to ensure that potential participants meet the inclusion and exclusion criteria.
5. If the participant is over the age of 50 years, his or her bone mineral density will be measured from dual-energy X-ray absorptiometry (DXA; Delphi W; Hologic, Inc.). Subjects will not be allowed to continue with the study if they have a total hip or femoral neck bone mineral density t-score < -2.5. The left hip will be evaluated unless the subject has had a left hip replacement. If both hips have been replaced, then the participant will not continue in the study. DXA scans will be performed by a State of Delaware certified radiation technician.
6. Falls self-efficacy will be determined by administering the Activities-Specific Balance Confidence (ABC) scale and the Falls Efficacy Scale – International (FES-I). Because the ABC scale dictates group assignment in our study design, this measure also serves as a screening tool.
7. We will administer the following surveys:
    a. Physical Activity Scale for Individuals with Physical Disabilities
    b. Center for Epidemiologic Studies Depression Scale (CES-D)
    c. A survey on the family and friend support for exercise habits
    d. Barriers to Physical Activity and Disability Survey
8. We will administer the following clinical evaluations:
    a. Berg-Balance Scale
    b. Abbreviated Balance Evaluation Systems Test (Mini-BESTest)
    c. Functional Gait Assessment
    d. Timed Up-and-Go test
    e. 10 m walk test
    f. Six-minute walk test
9. Reactive postural control will be quantified from anterior, posterior, and lateral single-stepping thresholds. Participants will be outfitted with a safety harness attached to an overhead rail. As they stand on a computer-controlled treadmill (ActiveStep®, Simbex, Lebanon, NH), participants will be instructed to “try not to step” in response to rapid

belt displacements. For each directionally-opposed pair of thresholds, a progressively difficult series of movements will be implemented. Here, thresholds are defined as the perturbation magnitudes that consistently elicits one or more steps in a given direction. Within each progression of perturbations, the direction and timing of the belt movement is pseudo-randomized to limit anticipatory adjustments. The progression of perturbations will continue until each opposite-direction threshold is identified, as evident by four consecutive failed responses.

10. Participants will be given a StepWatch™ activity monitor, and will be instructed on how to wear the monitor, when to wear the monitor, and how to return the monitor to the study team. Before leaving, we will ensure that the participant is able to don and remove the monitor strap on their own. Participants will wear the monitor for seven days.
11. After three weeks, participants will repeat all questionnaires, laboratory, and walking activity assessments (Steps 7-11).
12. After this second assessment, participants will undergo six sessions of perturbation-based fall-recovery training. Each session will consist of the following five-minute perturbation series.
    a. Standing perturbations that induce a forward fall, necessitating multiple steps to regain balance and remain on the treadmill. Separate series will focus on paretic and non-paretic steps. Participants will be instructed to "try not to fall".
    b. Standing perturbations that induce a backwards fall. Instructions will be to recover in a single step. This constraint is added because, unlike the multiple-step response of trip recoveries, slip recovery is dictated by first-step features. Separate series will focus on paretic and non-paretic steps.
    c. We will apply lateral perturbations, delivered as participants stand facing the side of the treadmill. Participants will be instructed to "try not to fall". We will apply left and right perturbations large enough to elicit a step.
    d. In two separate series, we will apply anterior and posterior perturbations as the participants walk. Our treadmill is equipped to deliver perturbations timed relative to foot strikes during gait.
    e. The training intensity, as determined by the perturbation size and, if applicable, gait speed, will be small at first, progressing to more challenging levels dependent upon participant performance, safety, and comfort. In other words, the size of the intensity will only be increased if the participant has a successful response, agrees to progress to the next intensity, and can do so safely, at the discretion of the research staff.
    f. For those participant who must use a cane, we will limit training to standing perturbations (parts a, b, and c). We will modify the perturbations to those just large enough to elicit a step or adjustment in the cane position.
    g. After each training session, the ABC scale and FES-I scale will be administered.
13. At the end of the six training sessions, participants will repeat all questionnaire, laboratory, and walking activity assessments (Steps 7-11). Participants will also be interviewed with open-ended questions and scales to determine the extent to which each aspect of the intervention was perceived as beneficial and challenging. In addition, we will record suggested changes and modifications to improve these perceptions and adherence.

Eligibility criteria for study participation include the following:

Inclusion criteria

- Participants must be 18 years or older
- Participants must have had a single stroke of non-cerebellar origin, occurring six or more months prior to study enrollment.

- An Activities-Specific Balance Confidence (ABC) score less than 68.
  Exclusion criteria (all self-reported)
- More than one stroke
- Acute illness at the time of functional assessment or training
- Body mass greater than 136 kg (300 lbs) to ensure that the treadmill accelerates accurately
- Lower extremity joint replacement or shoulder joint replacement within a year prior to participation
- Dementia
- Parkinson's disease
- A history of back surgery
- A history of neck surgery
- More than one occurrence of back or neck pain in the month prior to participation
- Current back or neck pain at the time of participant enrollment
- Bulging vertebral discs
- Spine, hip, or lower extremity fracture within a year prior to participation
- Open lesions on the lower extremity
- Insulin-dependent diabetes
- Use of a pacemaker
- Use of an ostomy pouch
- Pregnancy
- Osteoporosis
- The inability to stand and walk independently or with the assistance of a cane.
- Doctor recommendation to avoid moderate physical activity or exercise
- Any neural, muscular, or skeletal condition or injury that precludes safe participation in the training or introduces a confounding factor on the study, at the discretion of the clinician or study staff

Materials

Data sources will include anthropometric measurements, clinical measures of function, balance and mobility, stepping thresholds (a measure of reactive postural control), questionnaires about falls self-efficacy, depression, and physical activity, walking activity from step counters, and questions from interviews. All data will be acquired solely for research purposes. All materials will be identified by a subject-specific code, the key of which will be stored as a password protected file on a secure computer or server and/or in locked cabinets within the locked laboratory.

Potential Risks

It is possible that subjects could fall to the floor during assessments of mobility and balance. All participants will wear a harness attached to an overhead rail while on the treadmill. To minimize the risks of a fall during other assessments of balance and mobility, all subjects will be appropriately guarded using standard clinical judgment of safety procedures (e.g. use of a gait belt and/or harness system when needed, proper positioning of the rater relative to the subject, etc.).

Subjects may experience muscle soreness as a result of participation. Exclusion criteria have been determined in an effort to limit discomfort. In the case of acute soreness, the current training session will be ended, and subsequent sessions will not resume until

soreness has subsided. The perturbation magnitude will not be again advanced to the levels that initiated soreness.

Occasionally, subjects may feel a heightened level of excitement or nervousness during their participation. These feelings are usually due to the anticipation of an oncoming postural perturbation (i.e. there is a delay in time from when the subject says they are ready and the treadmill belts accelerate). A random delay in the perturbation onset, as well as no indication of the upcoming perturbation direction, are maintained in order to improve the ecological validity of the protocol (i.e. people are rarely aware of the timing and direction of a fall before it is initiated). Should the subject express these feelings, they will be given the option to end their participation in the session or study. Furthermore, accommodations such as frequent breaks, minimizing the delay before the perturbation, limiting the size of the perturbation, and allowing subjects to know the perturbation direction beforehand can be made. If the study team member determines that such feelings are unreasonably high, to the point where it precludes safe participation in the study, they will end the subject's participation in that aspect of the study.

During assessments and training sessions, we will stop participation if any of the following conditions occur: a) ataxia, dizziness, or near syncope, b) any chest pain or angina symptoms, c) Signs of poor perfusion cyanosis or pallor, and d) excessive fatigue, excessive shortness of breath, leg cramps, claudication.

For subjects who receive it, the DXA scan is accompanied by a negligible effective dose of radiation (0.001 mSv; www.radiologyinfo.org). This effective dose is less than 0.1% of the dose received from a spine X-ray, and it is comparable to the amount of radiation exposure from three hours in natural surroundings.

We consider the risks of our treadmill protocols to be minimal. The risks from these protocols are not greater than those encountered with exercise in the free-living environment. A harness system arrests the fall before the subject's hands, knees, or head come into contact with the treadmill. The subject may experience soreness from the harness support or from the required physical activity. The use of a treadmill to deliver perturbations to older adults, young adults, individuals with neuromuscular impairment, and individuals with lower-extremity amputations is well-documented in the literature. We will be using a commercially available, computer-controlled treadmill that is used clinically (CPT Codes: 97750, 97110, 97112, and 97116) for balance assessments and training (ActiveStep, Simbex, Lebanon, NH). Dr. Crenshaw and his laboratory have worked with over 250 individuals, including those with chronic stroke, those with lower limb loss, older adults, young adults, typically developing children, and children with cerebral palsy, on the ActiveStep with no serious adverse events or injuries requiring medical attention. Here, serious adverse events are defined as any untoward medical occurrence that results in death, is life threatening, requires insubject hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

We expect that those with low falls self-efficacy may frequently rely on a cane to stand and walk. Therefore, we have modified our treadmill protocols to be safe and feasible for use with a cane. Specifically, we have limited the standing perturbation sizes to those just large enough to elicit a step or an adjustment of the cane position. In addition, we have excluded these participants from perturbations delivered as the participant walks on the treadmill.

We see minimal risk of confidentiality—data are coded and no identifying information is used in any analyses or publication. We adhere to all HIPAA privacy rules that affect research protocols.

2. Adequacy of Protection against Risks

a. Informed Consent and Assent

For this study we will recruit seven individuals with chronic stroke from Delaware and adjacent areas in Maryland, Pennsylvania, and New Jersey. Subjects who complete the *Shared Pre-enrollment Process for Stroke Research Team Studies* protocol will be invited to participate in this study. The pre-enrollment study is a recruitment arm of the UD Stroke Registry. This registry advertises its studies through local media sources, social media, community outreach, and word of mouth.

Potential participants will be contacted by phone to explain the study, discuss and confirm inclusion and exclusion criteria, answer questions, and invite participation. If an individual is interested in participating, they will be invited to STAR Campus for the first study visit.

At this study visit, a member of the study team will guide the potential participant through an informed consent document, answering questions that the individual may have. Once written consent has been attained, the participant will be enrolled in our study.

b. Protection Against Risks

If immediate medical treatment is needed for any study related injury or adverse experience, the study Physical Therapist will evaluate the participant. If needed, the STAR campus emergency response protocol will be activated and first responders will come to the laboratory.

Each participant will be told that he/she has the alternative to not participate in this study, and that the choice to end participation will not jeopardize his/her medical care. The honorarium for the visit will still be paid. Insurance will not be charged.

All data are coded and no identifying information is used in any analyses or publication. A key linking identifiable data to subject codes will be stored as a password protected file on a secure computer or server, with physical copies stored in locked cabinets within a locked laboratory. We adhere to all HIPAA privacy rules that affect research protocols.

No study staff are qualified to clinically interpret incidental findings from the DXA scan. At the request of the participant, we will provide them with a printed copy of the DXA scan results that they can bring to their physician.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

The potential benefits associated with the project outweigh the risks of participation. Participants may learn more about their capabilities through participation in the assessments. Participants who receive a DXA scan may learn more about their bone density. The general knowledge gained by this study may inform hypotheses for subsequent studies to more rigorously evaluate the benefits of our exercise intervention on falls self-efficacy and walking activity. In addition, the current study will inform modifications to our approach to improve its feasibility. The participant-specific and general knowledge benefits outweigh the risks described earlier, including muscle soreness and nervousness/excitement. These risks are experienced in everyday life with the introduction of a new exercise program and when in

situations where balance may be challenged. However, in our study, the risks of falling to the floor or ground have been reduced by a safety harness and appropriate guarding from study staff.

4. Importance of the Knowledge to be Gained

We may develop methods to improve reactive postural control, increase balance self-efficacy, and enable walking activity in those with chronic stroke and low falls self-efficacy. If we are able to do so, then we may identify a pathway to enable walking activity, in turn improving the quality of life and healthspan of this population. These benefits outweigh the risks of participation, which align with risks of starting many other exercise programs (e.g. soreness, risk of loss-of-balance, nervousness/excitement).

Statistical Design and Power

This feasibility study has a single-arm, repeated measures design in which a non-active control period is followed by an intervention period. In other words, there are three assessment visits (baseline, assessment after non-active control period, and assessment after experimental intervention).

We expect to enroll seven participants into this study (Figure 1). Of these participants, we estimate that two will not pass initial screening from the physical therapist or DXA scan. Note that, in order to adhere with IRB and Radiation Safety guidelines, we must enroll participants before performing this screening.

The aim of this study is to demonstrate that fall-recovery training is feasible in stroke survivors with low falls self-efficacy. As per feasibility-study guidelines, we will gather evidence of the following:

- *Adaptation* will be documented by the changes in our protocol relative to our previous applications. Although we have proposed a specific training protocol, we anticipate that the need for further adaptation may become evident. Anticipated adaptations include limitations in the protocol duration, perturbation size, knowledge of the perturbation direction and timing, frequency and duration of breaks, and availability of hand support (handrail, cane, or research staff). By quantifying the number and magnitude of perturbations, as well as adherence to the protocol, we will evaluate how this adapted protocol compares to our previous version.
- *Implementation* includes the factors affecting the success and failure of completing the training. We anticipate that, despite proposed adaptability, participants may not complete all sessions. We will interview and survey participants to ascertain what aspects were perceived as challenging or beneficial, as well as to identify aspects that should be removed or changed to improve adherence and perceived benefit.
- *Limited Efficacy* will be evaluated with effect sizes (Cohen's d) of changes in self-efficacy and activity.

Given that this is a feasibility study, and not a design using inferential statistics, our sample size is not based on a power analysis. The results of this study may inform such analyses that support a subsequent grant application.