

MINIMAL RISK CLINICAL RESEARCH PLAN

Please complete: CPHS#

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- Respond to each item, even if to indicate N/A or not applicable
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1. Introduction and Background

Patients with Parkinson's disease experience impairments in the initiation and maintenance of walking, with decreased walking speed; small, shuffling steps; and 'freezing'. These gait impairments have been related to an inability to tilt the body forward enough to provide sufficient forward propulsion (Martin, 1963). In a previous study we demonstrated that the forward stepping times of patients with Parkinson's Disease were reduced following a five minute period in which they performed a simple non-invasive motor-training intervention called prism adaptation. Building on this proof-of-concept data, the present study will examine whether prism adaptation is a clinically viable rehabilitation tool for gait impairment. Using a double-blind, sham-controlled, randomized control design, we will examine whether consecutive daily sessions of prism adaptation for two weeks improves posture and gait in patients with idiopathic Parkinson's Disease. Forty patients will be randomly allocated to undergo either real or sham prism adaptation twice a day for two weeks. Posture and gait will be assessed before and after the intervention period using three sets of outcome measures: 1) standard clinical assessments, 2) Mechanized measurements and 3) self-report questionnaires. We hypothesize that, compared to patients who undergo sham prism adaptation, patients in the real prism adaptation condition will show reduced stepping initiation times, greater displacement of the body over the feet during stepping initiation, and increased self-report of confidence while walking.

Background. J. Purdon Martin (1963) described walking as 'controlled falling' in which the forward and downward shift in the body's centre of gravity is arrested by the action of the frontally positioned leg. Patients with Parkinson's disease show a reduced forward movement of the body relative to the feet during the initiation of walking (4,5), and this is thought to contribute to the decreased walking speed; small, shuffling steps; and 'freezing' that is characteristic of the disease. Indeed, the extent to which the forward movement of the body over the feet is impaired directly correlates with the severity of Parkinson's symptoms (5).

Postural imbalance is also seen in patients who suffer from left-sided hemiplegia following right-hemisphere stroke. Such patients frequently lean too far to the right while standing. Tilikete and colleagues (7) demonstrated that the rightward lean of stroke patients was corrected following five minutes of sensorimotor training using a technique called prism adaptation. During prism adaptation participants reach to targets that are viewed through prismatic lenses that bend the light before it reaches the eyes, shifting the visual image to one side. Since their movements are programmed based on shifted visual information, participants initially point to one side of the target. With successive trials, however, pointing accuracy is re-

established as movements are recalibrated in the direction opposite to the prismatic shift. For example, rightward-shifting prisms result in a leftward recalibration of pointing movements. This recalibration has been shown to have follow-on effects on sensory and motor performance in stroke patients that outlast the adjustment in pointing movements. Although improvements have frequently been observed following only one treatment session, research from stroke patients suggests that repeated sessions of prism adaptation (e.g., twice-daily, five-minute sessions for fourteen consecutive days) are required in order to impart sustained, clinically significant improvements in performance [4,14]. We propose to examine the effects of a two-week period of prism adaptation on posture and gait in patients with Parkinson's disease.

Previous research:

We previously tested the hypothesis that adaptation to upward-shifting prisms, producing a downward recalibration in pointing, would reduce forward stepping time in patients with Parkinson's disease. The rationale for this approach was that, based on the results of Tilikete and colleagues, adaptation to upward-shifting prisms would shift the standing posture forwards. In a study of 16 patients we found that a single five-minute session of prism adaptation reduced forward stepping time by an average of 183ms (~10% reduction) [4]. Backward stepping time was unchanged, and a test of adaptation to downward-shifting prisms with control participants showed no effect on forward or backward stepping. This study provides proof-of-concept that prism adaptation can reduce forward stepping time in patients with Parkinson's disease using a laboratory-based measure of stepping.

2. Objectives and Hypotheses

Objective: To compare the effect of two weeks of twice-daily adaptation to upward prismatic shifts in the visual field vs. two weeks of sham adaptation on measures of posture and gait in patients with idiopathic Parkinson's Disease.

Hypotheses: Compared to patients who undergo sham prism adaptation, patients who complete two weeks of real prism adaptation therapy will show reduced stepping initiation times, greater displacement of the body over the feet during stepping initiation, and increased self-report of confidence while walking. We will also measure a number of other common clinical indicators to determine whether prism adaptation improves motor performance and postural responses to external perturbations.

3. Study Design

Describe all study procedures, materials, and methods of data collection:

The study will have a longitudinal, repeated-measures, between-subjects, double-blind, sham-controlled design. Thirty patients with idiopathic Parkinson's Disease will be randomly assigned to undergo two weeks of twice-daily sessions of adaptation to upward-shifting prisms, or sham adaptation (in which patients perform the same sensory-motor task while wearing goggles fitted with neutral lenses). Measures of posture and gait (see below) will be recorded in two sessions: pre- and post-treatment. Additional long-term follow-up will be obtained through questionnaires by mail at one week, one month and three months post-treatment. The timeline for the research sessions, intervention period and follow-up questionnaires are outlined in Figure 1.

Procedures:

Randomization and blinding

Dr Bultitude will oversee the allocation of the participants to the control or treatment group and will be the only researcher who will not be blinded as to the experimental condition to which each participant belongs.

Participants will be allocated to the control or treatment group according to a pre-generated sequence of pseudorandom numbers, although deviations from this sequence may be made in order to ensure that the two groups are approximately matched in severity of symptoms. After prism adaptation training Dr Bultitude will give the participant the set of goggles that they will be using for their sham/real prism adaptation treatment. The goggles will be handed to the participant in a sealed, opaque bag so that none of the other researchers will be able to see what kind of goggles the participant has been given. The participant will be instructed to seal the goggles in the same bag when they bring them back to the Dartmouth Hitchcock Medical Centre at the end of the treatment period. Dr Bultitude will not be involved in any of the pre- or post-treatment assessments. In order to gauge progress an initial analysis will be performed once 60% of the participants have completed the post-treatment assessment, in which case the other researchers will be unblinded as to the group membership of the participants who have already completed the main components of the study. Aside from Dr Bultitude, the remaining members of the research team will be blind as to the group membership of the remaining 40% of participants.

Prism adaptation

Patients will undergo self-guided adaptation sessions in their own home, after initial training in the adaptation procedure by Dr Bultitude. Patients in the experimental condition will receive goggles fitted with prismatic lenses that induce a 15° upward shift in the visual image. Patients in the control condition will receive goggles fitted with neutral lenses. For each prism/sham adaptation session, patients will sit in a chair within reaching distance of a wall or cabinet upon which two dime-sized targets will be placed (one above the other, approximately ten inches apart). While wearing the goggles, patients will point rapidly to one target then the next, bringing their hand back to their torso between each pointing movement. They will be instructed to perform these movements ‘as quickly as possible’ for a total of 50 pointing movements (<5 minutes) in each treatment session. After performing 50 pointing movements the will remove the goggles. Each patient will undergo two daily sessions of prism adaptation for 14 consecutive days.

Assessment of Posture and Gait

Assessments of posture, gait, and activities of daily living will be performed by a Neurologist and a trained Physical Therapist at the Dartmouth-Hitchcock Medical Center on two occasions immediately before and immediately after the intervention period (the pre- and post-test). Three categories of outcome measures will be used; standard clinical assessments, mechanized measurements, and self-report questionnaires will be conducted by mail and/or phone on three further occasions (one week, one month and three months post treatment).

1) Standard clinical assessments.

Four commonly used clinician-scored evaluations will be used.

General Neurological Examination. This will be performed by a trained neurologist, and involves simple sensory and motor tests.

The Unified Parkinson’s Disease Rating Scale (motor component). Several dimensions of motor control are assessed by a clinician-scored evaluation. Patients are asked to perform simple tasks such as tapping their fingers as quickly as possible for five seconds, and their performance on each item is scored on a scale of 0 (“normal”) to 4 (“can barely perform the task”). The total score out of 92 is computed.

Timed Up and Go test. Starting from a seated position, the person is required to stand up, walk to a line 10 meters away, turn around, walk back and sit down. The person is timed.

Functional Gait Assessment. This is a reliable and valid assessment of assessing ten gait-related measures (e.g. stepping over a box, climbing stairs). A total score out of 30 is calculated, with lower scores indicating greater impairment.

2) Mechanized measures

We will use two sophisticated measurement systems to measure musculoskeletal factors related to posture and gait.

Assessment of postural stability using the SMART EquiTTest Balance Master. This system uses a force plate to measure center of gravity and postural control. Patients stand on a force plate while wearing a support vest. We will use two protocols provided by this system. The Motor Control test assesses the ability of the patient to recover their standing balance after an unexpected translation of the force plate. The Limits of Stability test measures the maximum distance a person can intentionally displace their center of gravity in a given direction without losing balance, stepping or reaching for their center of gravity in a given direction without losing balance, stepping or reaching for assistance. For both of these tests a comprehensive performance report is provided, including measures of reaction time and amplitude of movements.

We will also perform a third test that is not part of the standard EquiTTest protocol. For this, we will ask participants to take a step forward. We will measure the displacement of the center of gravity over the center of pressure (i.e., the movement of the body over the feet) using the same performance report as is used for the Limits of Stability test. This non-standard test will allow us to directly test our hypothesized mechanism of prism adaptation treatment: namely that it increases the displacement of the body over the feed when patients initiate walking.

Assessment of gait using the ActiveStep. This system is a mobility stimulator that enables safe measurement of walking and propensity to fall with and without environmental perturbations. A number of parameters are measured, including trunk extension and flexion velocity and step length and speed.

3) Self-report questionnaires

Four questionnaires will be used to measure patients' perceptions of their risk of falling and their confidence in safely performing daily activities. These will be administered five times: in the pre-test, post-test, one-week follow-up, one-month follow-up, and three-month follow-up.

Falls Efficiency Scale. This ten-item self-report questionnaire asks people to rate their confidence in performing daily activities without falling. Responses are given on a scale from 0 ("very confident") to 10 ("not very confident") and a total score out of 100 is computed.

Activities-specific Balance Confidence Scale. This 16-item self-report questionnaire is similar to the Falls Efficiency Scale, but has greater sensitivity to gait impairments in more ambulatory patients.

PDQ-39 (mobility and activities of daily living sections). This self-report questionnaire is the most widely-used Parkinson's Disease specific measure of health and daily function. Participants indicate the extent to which they have experienced problems with different aspects of mobility and self-care. Each item is scored from 0 ("never have problems") to 4 ("always have problems"), and a percentage is calculated.

New Freezing of Gait Questionnaire. This nine-item questionnaire detects and evaluates the impact and severity of freezing of gait on locomotion and daily activities.

The following questionnaire will be administered in the pre-test only:

Patient-Centered Outcome Questionnaire – Parkinson's Disease. This four-item questionnaire measures patient's expectations of treatment outcome. The data from this questionnaire will be used in post-hoc analysis to regress out any potential effects of patient expectation (e.g. placebo effect) on perceived improvements.

The following questionnaire will be administered in the post-tests only:

Post-intervention questionnaire. This questionnaire asks questions specific to the participant's experience of the prism adaptation treatment. There are two versions of this questionnaire. Version 1 is to be administered in visit 2. In Version 1 the participant is asked to rate the extent to which they felt any adverse effects, the

degree to which they enjoyed the treatment, and the extent to which they feel their symptoms have changed as a result of treatment. Version 2 is to be included in the post/telephone follow-up questionnaires and contains only the questions about the extent to which the participant feels their symptoms have changed as a result of treatment.

4. Analysis

Describe any qualitative tests and measures as well as quantitative methods:

All data will be anonymized and analyzed using non-parametric and parametric standard tests using SPSS software. Statistical analyses will be performed with appropriate correction for multiple comparisons.

The endpoints will be the post-treatment clinical assessment session.

Scores for each of the outcome measured will be analyzed using two-by-two, repeated measures ANOVAs, with Group (sham, prism) and session (pre, post) as independent factors. In the case of the self-report measures, two-by-four repeated measures ANOVAs will be performed with Group (sham, prism) and session (pre, post, one-month, three-months) as independent factors. Post hoc analyses will be in the form of t-tests (or non-parametric equivalents), corrected for multiple comparisons. These tests will determine if prism adaptation improves performance to a greater extent than sham treatment. In addition, 95% confidence intervals will be constructed around mean performance for each group before and after sham or prism treatment to test whether the group performance deviates significantly from established normative data or diagnostic cut-offs (e.g., for the UPDRS).

5. Study Progress Monitoring

Note: appropriate monitoring may include periodic assessment of the following:

- data quality
- timelines
- recruitment and enrollment

Provide a description of the methods which will be used to determine the progress of the study, including periodic assessments of data quality, timelines, recruitment, and enrollment as appropriate:

We will check into using the psychiatry DSMB.

6. Risks & Benefits

Note: Risks may be physical, psychological, social, legal, economic, to reputation, or others.

a. Describe any potential risks, their likelihood and seriousness:

There is a minor risk that the treatment or assessment procedures will result in some fatigue or discomfort. This is expected to be short-lived, and would be no greater than that involved in patients' normal physical therapy. To minimize the risk of fatigue during the pre- and post-treatment assessments, patients will be provided with breaks between tasks as required. Prism adaptation has been used for studying sensory-motor integration in healthy individuals for over a century, and in the treatment of stroke patients with hemispatial neglect for over ten years. In this time there have been no reports of serious adverse effects.

b. Confirm that risks to subjects have been minimized, by use of procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk:

Visual adaptation has a minimal risk: it is performed while seated, thus has the potential to provide a safe, indirect means to treat gait impairment.

c. Describe why all the risks to subjects are reasonable in relation to both anticipated benefits and the knowledge expected to be gained from the study:

The research is expected to lead to new insights into the treatment of gait problems in patients with Parkinson's Disease. Furthermore, it is possible that those patients who are randomly assigned to receive prism adaptation treatment will benefit individually by experiencing an improvement in gait initiation. All patients may also gain an increased understanding of their symptoms through the pre- and post-assessment sessions. Considering these potential benefits, the minor and unlikely risks involved in participation are reasonable.

7. Unexpected Events or Incidental Findings

Note: It may be important to consider the potential for certain unanticipated events to occur, for example:

- finding an anomaly in a MRI
- discovering child abuse
- causing distress in interviews of a sensitive nature

Describe potential events and provide a plan of action:

One item in the UPDRS includes depression with suicidality. If the patient is suicidal, we will escort subject to the ED for evaluation for depression.

8. Placebo Use or Inconsistency with Standard of Care

Does any part of this study involve the use of a placebo or procedures that are inconsistent with the standard of care at Dartmouth-Hitchcock Medical Center?

No Yes

If Yes, explain how the use of placebo or non-standard of care therapy may affect risks for participants, addressing the following:

- The safety and efficacy of other available therapies
- The maximum total length of time a participant may receive placebo on study
- The greatest potential harm that may result from not receiving or delaying effective therapy
- Safeguards for the participants receiving placebo or non-standard of care therapy

9. Genetics

Does any part of the study involve genetic analysis of biological specimens?

No

Yes, the study is based on the premise that a link between a genotype or a biomarker and a specific disease or condition is clinically useful in predicting the development of that specific disease or condition. **Please complete the [Genetic Research Form](#) and upload it to the ‘Supporting Documents’ page in Rapport.**

-OR -

Yes, the study is looking for an association between a genotype or a biomarker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve referral of participants to genetic counseling; however, participants will be informed of genetic testing in the consent form. **Please comment:**

10. Equitable Participant Selection

a. Estimated number of participants at Dartmouth CPHS reviewed sites:

Approximately 30 patients will be enrolled in the study at Dartmouth-Hitchcock Medical Center.

b. Provide a justification of the proposed sample size

For the methods specified above, there is no well-established method for calculation of group size as yet. We can, however, draw on experience from previous experiments, indicating what is the minimal/optimal number of participants for detecting significant effects. Previous studies that tested the effects of a similar prism adaptation treatment protocol on sensory and motor problems in stroke patients have used between 12 and 16 patients per group (Frassinetti, Serino). We aim to approach 40 patients with at least 32 completing the study (16 per group), which will provide a sufficient dataset even if up to 20% of participant withdraw before the completion of the study

c. Define the target population:

The patient population that will be targeted are the patient is referred for Parkinson's disease with gait impairment at Dartmouth-Hitchcock Medical Center

Inclusion/Exclusion Criteria:

Inclusion

- Diagnosis of idiopathic Parkinson's Disease
- Referral for gait training
- Aged 40-85
- If the subject is taking CNS-acting CNS-acting medications (benzodiazepines, hypnotics, antidepressants), regimen must be stable for 30 days prior to baseline visit
- Subjects with Stage II.5 – Stage IV (Hoehn and Yahr scale) where stage II.5 is bilateral involvement with axial involvement, but without balance difficulty, to Stage IV where one has severe disability but is still able to walk or stand unassisted.
- Subjects with any of the following abnormal scores (greater than 0) in the MDS-UPDRS Part III:
a) Part III.10 Gait; b) Part III.11 Freezing of gait c) Part III.12 Postural Stability
- Subjects with a Timed up and go test > 12 seconds

- Right-handed participants are preferred due to the cortical lateralization of functions related to sensorimotor adaptation and postural control. However we will recruit left-handed participants if there are insufficient right-handed volunteers.

Exclusion

- Subjects with a known psychiatric comorbidity that in the investigator's opinion would compromise participation in the study
- Subjects with a neurologic diagnosis, other than Parkinson's disease that can cause imbalance and gait impairment. (e.g., multiple sclerosis, stroke, subdural hematoma, peripheral neuropathy)
- Injury or impairment to the right arm (other than that which is due to Parkinson's Disease) that would affect pointing movements
- Subjects with normal score on UPDRS part III
- Classified as legally blind or lacking sufficient visual acuity to view the target and pointing hand during prism adaptation.
- Lacking sufficient understanding of verbal and written information in English to complete any of the consent screening forms

d. Vulnerable populations

Note: Certain populations are considered vulnerable to coercion and undue influence and are provided with additional protections when participating in a research study.

Identify any of the below populations which you plan to recruit for this study. In addition, complete the form(s) linked with each population as necessary and upload on the 'Supporting Documents' page in Rapport.

- [Pregnant Women, Fetuses and Neonates](#)
- [Children](#)
- [People with impaired decision-making capacity](#)

The following populations may also be considered vulnerable to coercion or other undue influence:

- Prisoners
- People who are economically disadvantaged
- The elderly
- People who are illiterate or do not speak English
- Students and employees

Describe any other potentially vulnerable population(s) and the additional protections provided to them:

Not applicable. We will be recruiting the elderly but will not be excluding people regarding socioeconomic status.

11. Recruitment

Describe method(s) of recruitment. Associated advertisements and other materials to be used for recruitment should be uploaded to the 'Consent Forms and Recruitment Materials' page in Rapport.

Subjects will be recruited from those who had been referred for gait evaluation for Parkinson's disease at Dartmouth-Hitchcock Medical Center

12. Informed Consent, Assent, and Authorization

All forms discussed in this section should be uploaded to the ‘Consent Forms and Recruitment Materials’ page in Rapport

a. Please describe the consent and/or assent process, addressing the following:

- Who will obtain consent/assent from participants
- Where the consent/assent process will take place
- The timeframe for providing information potential participants about a study, having the consent form signed, and beginning study activities
- Any precautions taken to minimize the possibility of coercion or undue influence
- The forms which will be used as well as any aids used to simplify scientific or technical information
- How comprehension will be ensured

The PI will be the only person obtaining consent. Once the patient is interested in the study and meets criteria, the informed consent will be sent to them for the proper review prior to coming for their first visit. If the patient does not speak English, the use of a translator will be made available by DHMC to review the consent with the patient and make sure all questions have been answered appropriately. Aids such as drawing or diagrams are sometimes used if the patient needs visual assistance to understand an answer to a question.

b. Waiver(s) or alteration(s) may be requested for research that involves no more than minimal risk.

Indicate requested waiver(s) or alteration(s) below. In addition, complete the corresponding section of the [Waivers and Alterations Request Form](#) and upload it to the ‘Consent Forms and Recruitment Materials’ page in Rapport.

- For the informed consent process
- For the documentation of informed consent
- For the HIPAA Authorization to use and/or disclose PHI
- For a waiver of the requirement for medical record documentation

13. Financial impact on participants

a. List the tests, visits, and procedures performed for only research purposes and specify who will pay:

Note: Research procedures may not be billed to a health insurance plan

All exams, visits and procedures for only research purposes will be funded by a grant from the Hitchcock Foundation.

14. Compensation or Gifts

Please describe any payments, gifts or reimbursements participants will receive for taking part in the study:

Participants will not receive any reimbursements for taking part in the study.

15. Privacy of Participants

Note: Methods used to obtain information about participants may have an effect on privacy. For example:

- Consent discussions or interviews held in public which concern sensitive subjects or behaviors
- Observations of behavior, especially illicit behavior, in quasi-public settings

Describe any activities or interactions which could lead to a breach of privacy and provide a plan to protect participant privacy:

N/A

16. Confidentiality of Data

Note: Any person engaged in research collecting information about illegal conduct may apply for a [Certificate of Confidentiality](#) from the National Institute of Health.

a. **If disclosed, could any of the data collected be considered sensitive, with the potential to damage financial standing, employability, insurability, or reputation?**

No Yes

If Yes, describe the data or information, the rationale for their collection, and whether a Certificate of Confidentiality will be obtained:

b. **Describe the safeguards employed to secure, share, and maintain data during the study, addressing any of the following which may apply:**

- Administrative, ie. coding of participant data
- Physical, ie. use of locked file cabinets
- Technical, ie. encrypted data systems

For purposes of this study, the data will be identified through the use of patient's initials and randomized code number. The study team will transfer the data via computer. This information can only be transmitted by the PI (s) or the coordinator for this study. Both the study doctor and the coordinator have each a different number coding as well as a password for the protection of computer and electronic files. Any source documents are kept in a locked room or cabinet.

c. **Describe the plan for storage or destruction of data upon study completion:**

Upon study completion, data will be stored in a locked area. If the data is destroyed, it will be shredded in a secure area