Evaluation of a Spasticity Management Program for People with Multiple Sclerosis

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Specific Aims/Purpose
Our *long-term goal* is to determine if the MS Spasticity: Take Control (STC) program of education and stretching improves quality of life and functional outcomes in people with Multiple Sclerosis (PwMS). The *overall objective* of this application, which is the next step toward attainment of our long-term goal, is to determine if STC improves the *impact and severity* of spasticity as well as other patient reported outcomes in PwMS. We will accomplish this with the following specific aims:

Specific Aim #1: To evaluate the STC program on the impact and severity of spasticity and other patient reported outcomes in ambulatory adults with MS and spasticity. This will provide the fully powered evaluation of the STC program compared to a comparison program. Outcomes will include measures of the impact and severity of spasticity, fatigue, mood, the impact of MS on walking and daily activities and the frequency of participation in stretching for MS lower extremity spasticity in ambulatory adults with MS and spasticity.

Specific Aim #2: To determine if the effects of STC are sustained for 6 months. This will provide information about ongoing participation in stretching and durability of effects on the above measures.

It is expected that these aims will inform us if the STC program with home stretching is beneficial in the short-term, after one month of home stretching, and in the medium-term, after six months of home stretching, compared to a comparison program.

If effective, STC could be adapted to a web-based program for on-demand self-study, modified for people with greater severity of MS and adapted to address spasticity in other neurological conditions that cause spasticity that are also costly to the VA such as traumatic brain injury, spinal cord injury and stroke.

Due to the COVID-19 pandemic in 2020, we have adapted the original STC program to be delivered remotely through a VA-approved video conferencing platform in addition to in-person.

A) Hypotheses

1) Primary hypothesis: We hypothesize that, for PwMS who have spasticity, the STC education and exercise program, in conjunction with home practice, will reduce the *impact* of spasticity more than a comparison program with home practice using the National MS Society (NMSS) stretching brochure. The primary outcome measure will be the *impact* of spasticity as measured by the MS Spasticity Scale 88 (MSSS). (1-2) The primary endpoint of the study will be following participation in either intervention and one month of home stretching.

2) Secondary hypotheses:

a) We hypothesize, in PwMS and spasticity, that the STC program, in conjunction with home practice, will reduce the severity of spasticity, altered mood, and the impact of MS on walking and daily activities more than a comparison program with home practice using the NMSS stretching brochure. The severity of spasticity as measured by the Numeric Rating Scale for Spasticity (NRS) will be a secondary outcome measure. (3) These outcomes will be collected at the primary endpoint following one month of home stretching.

b) We hypothesize that effects on the impact and severity of spasticity and other patient reported outcomes will be sustained or improved for six months in the STC participants but not in the comparison program participants. Measurement of all outcomes following six months of home stretching is our secondary endpoint.

c) We hypothesize that STC participants will report more participation in stretching for MS lower extremity spasticity than comparison program participants on a daily diary of stretching participation.

A. Scientific Rationale and Significance

1) Spasticity is common in PwMS with significant impact on activity, participation and quality of life. Spasticity is identified by increased resistance to passive stretch and is a result of changes in the central nervous system. The most commonly used definition of spasticity proposed by Lance in 1980, “Spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome,” is not patient-centered. (4) Spasticity in MS is thought to result from demyelination and/or axonal degeneration in descending central nervous system motor tracts (corticospinal, medial reticulospinal, lateral vestibular and dorsal reticulospinal tracts) causing disturbances in the inhibitory interneurons in these pathways. (5-6) A patient-centered description of spasticity was used for the North American Research Committee on MS (NARCOMS) registry: “unusual tightening of muscles that feels like leg stiffness, jumping of the legs, a repetitive bouncing of the foot, muscle cramping in the legs, or the legs going out tight and straight or drawing up.” Registry analysis (n=20,969) found ~6500 people with minimal spasticity (spasticity is noticeable but does not interfere with activities), ~4000 people with mild spasticity (spasticity forces changes in activities once a week or less),

~3600 people with moderate spasticity (spasticity interferes with activities several times per week), ~2700 people with severe spasticity (spasticity forces modification in activities every day), and ~800 people with total spasticity (spasticity prevents activities every day). In total, 84% of these registrants were dealing with spasticity every day. (7) Most sources report 60-80% of PwMS have spasticity. (7-9) MS spasticity is worse in men who are also more likely to be disabled and unemployed. Spasticity worsens with longer disease duration and greater disability. Quality of life worsens as spasticity worsens. Healthcare utilization increases with spasticity severity. 78% of NARCOMS respondents take one drug for spasticity. 45.9% take two or more drugs for spasticity. (7) 20% of participants in a Swedish quality of life with MS and spasticity survey rated their quality of life as worse than death. (10) Thirty years of data collection by NARCOMS found progression of the severity of spasticity reported by survey respondents parallels progression of gait disability, emphasizing the progressive nature of spasticity with increased disease duration and disability and the importance of addressing spasticity as a means to slow or reverse disability. (7, 11) The mechanisms underlying spasticity are complex and not fully understood, particularly when spasticity is combined with other symptoms such as weakness. MS-related spasticity contributes to MS disability with gait disorders, falls, fatigue, spasms, pain, and may hasten the time to wheelchair dependency. (7-9, 12-14) The increased disability and dependency may lead to social isolation, depression, cardiovascular disease, muscle fibrosis and joint contracture. These in turn can lead to skin breakdown, osteomyelitis, sepsis and death. Treatment for these complications is expensive for health insurers and society and painful for the affected individuals. (7-9, 10, 15)

2) Treatment of spasticity is expensive. A German study reported the average financial cost for PwMS with mild spasticity as 2,268 Euros per year (~$3016 US) and nearly quadrupling to 8,688 Euros per year (~$11,555 US) for PwMS and severe spasticity. (15) A Swedish study of resource utilization by PwMS and spasticity found healthcare costs relatively stable (7% of total costs) even as spasticity worsened in their sample of more disabled people who had limited walking ability as an entry requirement (median disability in the study was need for bilateral assistance for daily walking) and moderate spasticity. Direct non-medical costs (housing adaptations and help, personal assistance and informal care) and indirect costs (patient and caregiver productivity losses) accounted for the balance of the 114,293 Euros per year (~$152,000 US). (10)

A 4-country meta-analysis found 56% of PwMS fall and 37% fall frequently. A primary progressive course of MS was associated with significantly increased odds of falling (odds ratio (OR) 2.02; CI 1.08-3.78). Fall risk peaked at EDSS levels of 4.0 and 6.0 with significant ORs between 5.30 (2.23-12.64) and 5.10 (2.08-12.47). (12) Knowing spasticity contributes to falls, spasticity is worse in people with longer disease duration and the overall population of PwMS is older, we must consider the cost of falls in the cost of spasticity. The Center for Disease Control reports in older adults:

- “Each year, millions of people 65 and older are treated in emergency departments because of falls. (16)
- “Over 700,000 patients a year are hospitalized because of a fall injury, most often because of a broken hip or head injury. (16)

- “Fall injuries are among the 20 most expensive medical conditions. (17)
- “The average hospital cost for a fall injury is $35,000. (18)
- “The costs of treating fall injuries increase with age.” (18)

Spasticity contributes to contractures and skin breakdown, therefore, the cost of pressure ulcers is also reasonable to consider in the cost of spasticity. The Agency for Healthcare Research and Quality reports:

- “Number affected: 2.5 million patients per year.
- “Cost: Pressure ulcers cost $9.1-$11.6 billion per year in the US. Cost of individual patient care ranges from $20,900 to $151,700 per pressure ulcer. Medicare estimated in 2007 that each pressure ulcer added $43,180 in costs to a hospital stay.
- “Lawsuits: More than 17,000 lawsuits are related to pressure ulcers annually. It is the second most common claim after wrongful death and greater than falls or emotional distress.
- “Pain: Pressure ulcers may be associated with severe pain.
- “Death: About 60,000 patients die as a direct result of a pressure ulcer each year.” (19)

3) Anti-spasticity agents are first line treatments for spasticity. A 2003 systematic review of anti-spasticity agents - oral agents, intra-thecal baclofen and botulinum toxin injections – concluded: lack of understanding of spasticity and the ability to measure it resulted in inconclusive results in the majority of trials. Using a common assessment – the Ashworth scale or Modified Ashworth scale (MAS) – only three studies showed benefit of oral medications over placebo and none of the comparative studies showed a difference between drugs. They concluded there was no good evidence to recommend one agent over another or newer agents over older agents. They state there is *an urgent need for better assessment tools that correspond to the daily patient experience and then perform good quality studies. In addition, they felt it was imperative to not just study medications but to also investigate non-drug spasticity management approaches.* (20) In addition to limited effectiveness, current spasticity medications have many undesirable side effects such as sedation and drowsiness, nausea and vomiting, lightheadedness, dry mouth and weakness. (7-9, 20) Likewise, the newest oral drug, Arbaclofen Extended Release Tablets, showed benefit against placebo but not against the traditional oral form of baclofen. (21)

4) Skilled rehabilitation, exercise and stretching are first line treatments for spasticity. Skilled physical and/or occupational therapy for exercise and regular stretching are often recommended to delay the need for or combined with medications to manage spasticity. (8) A small study of 30 PwMS and spasticity in the quadriceps found significant improvement on the MAS with oral baclofen and baclofen combined with stretching exercises compared to placebo or placebo with stretching exercises. Adding stretching exercises to baclofen treatment resulted in a trend for further benefit. (22) A physical therapy group exercise intervention in Turkey with flexibility, range of motion, strengthening, core stabilization, balance, coordination and functional activities found significant improvement in spasticity with the MAS in 3 bilateral muscle groups of

exercisers compared to those wait-listed. (23) A group recently measured four different but common positions to stretch the ankle plantar flexor muscles. They measured ankle torque, muscle lengthening, muscle activation on both sides of the joint, duration subjects could hold the stretches and reports of sense of safety while performing the stretches. They found evidence of potential stretching benefit in this muscle group. (24) In a 1992-93 survey of Consortium of MS Centers (CMSC) practitioners in North America, 93% (14 of 15) reported stretching was effective and used frequently for MS-related spasticity without research evidence. (25) This support was likely based on the earlier study and empirical belief that stretching was the realistic and practical means to maintain range of motion in a condition causing involuntary muscle contractions. Muscles shorten when they contract. Therefore, it seems logical to apply the opposite condition, i.e. stretching or elongating muscle tissue, to counteract the shortening effect of the spasticity contracting stimulus. Subsequent documents, including the Spasticity Guideline, continue to recommend stretching with the same minimal evidence. (8) Stretching continues to receive little mention. One sentence in the NARCOMS Registry report of prevalence and treatment of MS spasticity mentions stretching and states, “a little over one half of the respondents used physical therapy or a stretching regimen to alleviate their spasticity.” This is not clear if physical therapy and stretching are considered the same or different interventions. (7) A 2013 Cochrane Review of non-pharmacological interventions for spasticity in MS only mentioned stretching combined with botox injections. (26) A recent systematic review of effects of stretching for spasticity found 21 articles, one in MS. Four of the 10 Class 1 studies had control groups, none in MS alone. A meta-analysis was not feasible due to methodological and other differences between the studies. Reviewers found the available evidence was inconclusive on the clinical benefit of stretching for spasticity of any origin. They emphasized that future research in the field of stretching for spasticity provides a *clear paradigm for stretching, appropriate outcome measures and clinical importance.* (27) Recommendations for spasticity and contracture prevention and management typically recommend skilled physical and occupational therapy. (26, 28-29) The mainstay of a skilled therapy program for spasticity is stretching, with the same lack of evidence noted above, in addition to positioning, orthotics, casting and other interventions. (26, 29)

5) Second line treatments for spasticity are botulinum toxin injections, intra-thecal baclofen (ITB) and steroids. Intramuscular botulinum toxin type A is approved for the treatment of upper limb spasticity since 2010 and was recently approved for ankle and toe muscles of the lower extremities. (30) It requires injection, temporary paralysis and, if effective, repeated administration with associated inconvenience, cost and discomfort. (31) Surgical procedures such as ITB have shown benefit to manage severe spasticity in PwMS. (8, 32-34) However, it is often not used until the person is no longer walking. ITB has associated high cost, surgical complications and inconvenience and need to return for refill medications or risk life-threatening consequences. **(**32-34) A recent trial of intra-thecal steroid injections administered 3-5 times every other day along with physical therapy showed benefit for treatment resistant spasticity but needs further evidence and means for practical application. (35) Regular and consistent stretching may be able to prevent or delay need for these treatments and is believed to

remain necessary for comfort, hygiene and minimizing deformity and other complications, even with these interventions.

6) Cannabinoids may be add-on treatments for spasticity. Cannabinoids are now recommended in Europe as an add-on treatment for moderate-severe treatment-resistant spasticity. (36) A recent Neurology guideline urged caution for using cannabinoids in MS. (37-43) Cannabinoids and medical marijuana have historically been illegal in the US and therefore not allowed in the VA. However, on May 16, 2016 the US House of Representatives voted to allow VA doctors to discuss and recommend medical marijuana in states where it is presently legal (25 states and District of Columbia) by a vote of 233-189. (44) A Senate committee adopted the same by a 20-10 vote. (45) Cannabinoids and marijuana are unlikely to be recommended as first line treatments due to concerns about side effects but may become add-on treatments as utilization increases. (46)

7) Studies have been done on the effectiveness of stretching. Stretching is the process of elongation via applied tension to the soft-tissue structures of muscle, tendon, connective, vascular, dermal and neural tissue. This tension and resulting elongation may change viscoelastic, structural and excitability properties in the stretched muscle. (24, 27-28) The goals of stretching for spasticity are to normalize muscle tone, maintain or increase soft-tissue extensibility, decrease pain, and improve function. A meta-analysis by the Cochrane Collaboration concluded "Stretch does not have clinically important effects on joint mobility in people with, or at risk of, contractures if performed for less than seven months. The effects of stretch performed for periods longer than seven months have not been investigated." (28) A systematic review by the same authors stated no conclusions "could be made about the effects of stretch on quality of life or participation restriction" in neurological conditions. (29) While they concluded stretching for less than 7 months has not been shown to be effective, they do not offer alternatives or other solutions for maintaining range of motion, comfort and function. An earlier systematic review concluded stretching protocols were generally inadequately described and poorly standardized. (27) Clinical judgment and lack of other better evidence suggests that it makes sense to stretch in the presence of spasticity. *Spasticity is an involuntary stimulus to muscle tissue to contract or shorten as part of the upper motor neuron syndrome. Joint range of motion is lost at the extremes of motion first and eventually resulting in contractures if motion is unrecoverable. Contractures have been identified early in people with mild MS. (47) In light of the relentless progression of the disease process of MS, worsening of symptoms and problems like spasticity and worsening quality of life with increasing spasticity (8), it behooves us to continue searching for effective strategies to maximize function, comfort and quality of life for Veterans and others with MS and spasticity.*

8) What are we measuring? How are we measuring it? The Ashworth (48) and the Modified Ashworth scales (MAS) (49) are the most commonly used assessments to quantify spasticity. They provide reproducible assessments of spasticity but validity has been seriously questioned. Both report subjective *examiner* ratings of passive resistance to quick stretch. While simple and reproducible, both are criticized that they

are subjective and capture only one component of spasticity: resistance to passive movement. Evidence suggests there is more than passive movement to spasticity including level of activity (voluntary and reflex) in the alpha motor neuron of agonist and antagonist muscle groups and the viscoelastic properties of joints and soft tissue. Individuals with upper motor neuron lesions may also be influenced by reflex excitability, perception of movement, changing tone, temperature and speed of applied movement. (4, 50) The Ashworth and the MAS are quick and relatively easy to use clinically but still rarely used. (50) More complex assessments, less likely to be used clinically, have mixed results and may be limited to one muscle group due to complexity. (22, 51)

9) New patient-centered outcome measures have been developed. In response to the Spasticity Guideline and criticisms of the Ashworth and MAS, new tools have been developed to capture the patient's perspective of spasticity. We have chosen patient reported outcomes due to criticisms of the Ashworth and MAS. It is important to note that patient reported outcomes using validated measures have been used successfully in research on patients with pain and depression (52). In both cases, treatments have been developed and proven to be efficacious using patient self-reports. Also, both the NIH and the FDA are putting increased emphasis on patient reported outcomes in clinical trials even in disorders for which there are objective measures. We feel the criticisms of the Ashworth and MAS justify not using them and using these new alternatives. (20, 53-54)

a) The MS Spasticity Scale 88 (MSSS) is a valid and reliable measure of the *impact* of spasticity in PwMS. (1) The MSSS was developed as a patient-focused measure to capture patient experience and perception of the *impact* of spasticity in MS with day-to-day symptoms and during functional activities. It quantifies spasticity in eight clinically relevant areas: spasticity specific symptoms (muscle stiffness, pain and discomfort and muscle spasms), areas of physical functioning (activities of daily living, walking and body movements), emotional health and social functioning. It highlights the complexity of this seemingly one dimensional concept. Extensive testing, analysis and evaluation supported the need for the eight scales to cover the breadth of the problem. The total score can be used and each of the subscales is a stand-alone measurement so it is appropriate to report total and subscale scores. The authors acknowledge that this new tool contributes little to improve our understanding between this self-assessment and objective clinical findings but their goal was to create a useful tool to move the field forward for improving patient's status and quality of life. We plan to use the MSSS as the primary outcome measure in the proposed trial of STC to capture the *impact* of spasticity. (1) The MSSS validity and reliability was confirmed in a German study. (2)

b) The Numeric Rating Scale for spasticity (NRS) is a valid and reliable measure of the *severity* of spasticity. (3) The NRS was developed, has established validity, reliability, and evidence of clinically important change. NRS, like the MSSS, was developed to capture information from the patient perspective. NRS measures *severity* of spasticity on a 0-10 scale with 0=no spasticity and 10=worst possible spasticity. The test-retest reliability was considerably better than the Ashworth (ICC 0.83 vs 0.53). Validity was supported by a consistent association with the Patient Global Impression of

Change (PGIC) scores. 29.5% improvement was indicative of “much improved” or better on the PGIC, consistent with the widely used Numeric Rating Scale for pain showing 30% improvement is clinically important. The 18% Minimal Clinical Important Difference (MCID) was consistent with 10-20% improvement in pain recognized as the MCID for pain. (3) We plan to use the NRS to capture *severity* of spasticity as a secondary outcome measure in place of other severity scales.

10) Preliminary data support the value of self-management interventions in MS. Self-management strategies, including learning and practicing skills to continue satisfying life activities, are increasingly important for improving quality of life in chronic conditions like MS. (55-56) A systematic review on self-management in neurological diseases from 1990 to 2008 and found one Class I, one Class II and seven Class III evidence articles in MS. They concluded that more rigorous controlled trials are warranted and include a table of proposed methodological strategies. (55) The present proposal meets their methodological recommendations. In 2009 the Consortium of MS Centers published a white paper on *Patient Self-Management in MS* to encourage application of self-management strategies in clinical care as well as research. (56) MS Spasticity: Take Control is a self-management program with education about spasticity and options to create a specific lower extremity stretching program for daily use. Consistent with adult education and cognitive behavioral therapy principles, empowering people with chronic conditions like MS to implement their own treatment path is important to lifelong disease management to mitigate disability and improve outcomes.

Significance of the proposed research

Stretching to maintain tissue and joint range of motion is the cornerstone treatment for spasticity of any origin and any severity, including MS. Empirical evidence, expert opinion (8) and one small study from 1991 (22) constitute the evidence for stretching for MS-related spasticity. The contribution the proposed research is expected to provide is evidence for the benefit of stretching for MS lower extremity spasticity. *This contribution will be significant because it will be the first fully powered study examining stretching for the treatment of lower extremity spasticity from any cause.* This will then allow the ability to compare the benefits and side effects of stretching to other spasticity treatments such as medications, injections, surgery and alternative approaches (i. e. cannabinoids) and evaluate effects on morbidity and mortality, activity participation and quality of life. If stretching is shown to be beneficial, group delivery will be more time efficient and cost effective for the VA than one-on-one physical therapy. These results will set the stage for delivering stretching by other means, such as web-based via the internet, and developing similar programs for other conditions that cause spasticity that are also important to the VA such as traumatic brain injury, spinal cord injury and stroke.

Innovation of the proposed research

Lack of a standardized program for stretching has been one of the main reasons progress in MS spasticity treatment has been stalled for over 20 years. (20, 25, 27) We have created a self-management program for MS spasticity with education and a standardized stretching component that is supported by a DVD demonstrating the stretching exercises and manuals with pictures and written descriptions of the stretches that has initial efficacy from our pilot trial of STC (Work Accomplished section B Preliminary results)*. The proposed research is innovative, in our opinion, for three reasons. First, we will use STC, the first formal program developed from the Guideline that is specifically for MS-related spasticity. Second, while standardized, the stretching component of STC offers choices for stretches that allow developing a customized program to meet individual needs, something historically requiring one-on-one physical therapy. And third, we will evaluate this new program using the improved patient reported measures for the impact and severity of spasticity from the patient perspective and not from the examiner perspective.* Self-management programs are needed in chronic diseases for cost-effectiveness and personal control. (55-57) To our knowledge, this is the first self-management program for MS-related spasticity and the first to have initial efficacy.

B. Preliminary Studies

1) The PI is a physical therapist with over 25 years of experience working with PwMS, including teaching stretching exercises to hundreds of PwMS, caregivers of people with advanced MS and people with other neurological or orthopedic conditions.

2) The multidisciplinary, multi-stakeholder "What Do We Know in MS?" conference. In 1992 the PI was a member of the physical therapy panel for management of MS spasticity. Important gaps were identified: 1) minimal evidence exists beyond belief that regular stretching reduces spasticity, improves functional mobility and helps to prevent complications such as contractures and 2) better measures of spasticity are needed to capture spasticity from the patient's perspective. Questions endorsed to drive future research: "1) Does a program of daily stretching result in decreased severity of spasticity? 2) Does a program of daily stretching result in improved functional mobility?" remain unanswered. (25) Several gaps are now filled. The *Spasticity Management in MS* guideline recommends comprehensive and consistent treatment for spasticity. (8) The MSSS captures the patient's perceived *impact* of spasticity in day to day functioning. (1, 2) The Numeric Rating Scale for spasticity (NRS) is a validated measure for *severity* MS spasticity from the patient perspective. (3) STC, a standardized program for spasticity education and stretching instruction now exists with evidence of feasibility and initial efficacy in ambulatory adults with MS and spasticity (see sections 5-8 below.) The conference questions are still relevant and, if funded, the proposed study will provide initial answers and *complete this next step* to move the field forward.

3) The MS Council for Clinical Practice Guidelines publishes the *Spasticity Management in MS* clinical practice guideline in 2003. The PI was the American Physical Therapy Association representative on the MS Council for Clinical Practice

Guidelines. Spasticity was chosen as an important symptom due to the severity and prevalence of spasticity in PwMS, lack evidence for treatment with current agents and techniques and inconsistency of treatment throughout the disease course. (8)

4) The proposed study follows the investigators' successful model to study *Fatigue: Take Control*, the NMSS implementation program for the *Fatigue and MS* clinical practice guideline. The PI for this study created a DVD-based self-management program *Fatigue: Take Control* (FTC) in partnership with the NMSS. (58-59 The NMSS pilot trial of FTC with Ms. Hugos as PI resulted in a peer review publication (58) and a multicenter Veterans Administration (VA) Merit Review grant with Ms. Hugos and Dr. Dennis Bourdette to study the program in a fully powered study. Data collection for the multicenter trial is complete and manuscripts are in progress. We presented a poster at the European Committee on Treatment and Research in MS (ECTRIMS) where it won a "Top Score Poster" award for the top 8% of 1300 posters. (60) The present trial replicates this successful research model.

5) *MS Spasticity: Take Control* (STC) is created by the proposed PI as an implementation program for the *Spasticity Management in MS* clinical practice guideline. It included the following components:

a) A 28-minute DVD with education and information about MS-related spasticity features MS professionals and poignant stories by PwMS and includes the following topics:

- recognizing spasticity;
- quality of life and the importance of behaviors and tools to maintain independence and participation;
- recognizing spasticity triggers;
- treatment of mild spasticity with stretching and other exercises;
- treatment of mild to moderate spasticity with medications, stretching and other exercises;
- treatment of moderate to severe spasticity with Botox injections and/or intrathecal baclofen pump in addition to stretching and possibly medications;
- treatment of mild/moderate/severe spasticity with complementary and alternative treatments (relaxation, massage, acupuncture, meditation, yoga and different diets, but excluding cannabinoids);
- a message about the importance of taking control of MS spasticity for overall health and quality of life.

This program does not address other possible surgeries for treatment of severe intractable spasticity. Ablative and/or orthopedic surgical procedures were beyond the scope of the intention of this program for mild to moderate spasticity for ambulatory PwMS and spasticity. Following review by other therapists and physicians, this DVD was promoted on the websites of the VA MS Centers of Excellence and the CMSC.

b) A 20-minute lower stretching DVD teaches a standardized, yet individualized, program of stretching for MS-related spasticity. Eight body areas are targeted and several alternatives positions are provided for the stretches with the goal of each person

finding at least one exercise in each group they can do regularly for an approximately 15-minute per day stretching routine. The exercises are:

- 'elongate' the whole body as a preparatory relaxation exercise;
- two choices each for trunk rotation, inner thighs, upper calves, lower calves and hip flexors/extensors;
- seven choices for hamstring,
- eight choices for quadriceps.

The choices provide options for positioning for more comfort and ease of completing the exercises and as options for easier or more challenging stretches. The options are not designed to be a progression although some could be considered progressions with positions that are easier initially for tight muscles and then changing to other positions as the muscles become more flexible and the person is familiar with the exercises. Likewise, easier options are available if MS worsens. *Any one of the exercises in each group is sufficient to provide an adequate stretch when applied as instructed, in nearly anyone with MS of any ambulatory ability.* For instance, there are hamstring and quadriceps stretches lying down and sitting that do not challenge balance. Standing options for hamstrings and quadriceps may challenge balance excessively for some, increasing risk of falls so would not be appropriate. The standing calf stretches are in the same positions that MS subjects preferred in the recent study measuring torque applied in plantar flexor stretching for providing a strong but safe stretch. And the sitting position was found to be the stretch that PwMS could hold the longest (5 minutes sitting compared to 2.5 minutes standing), both exceeding the 30-60 seconds recommended in STC indicating subjects should be able to meet the 30-60 second STC recommendations. (24)

c) Participant manuals include written information for reference. Manuals include all the information in the first DVD, learning objectives, a glossary of terms, space for notes and personal reflections and still photos with written instructions for all the stretches included in the second DVD.

d) The facilitator manuals help with organizing and leading the class sessions. In addition to the information in the participant manuals, the facilitator manuals have class agendas and tips to keep the group sessions running smoothly. (See Appendix)

6) STC includes the recommendations for a *standardized* program from the 2008 systematic review on stretching for spasticity. (27) Participants are instructed as follows in the DVD, manuals and classes: "Keep breathing and do not hold your breath when stretching. Drink plenty of water throughout the day. When you stretch, you should feel a gentle pull but no pain in the muscles being stretched. Proceed slowly until you feel the gentle pull. Pain is a protective response to overstretching. On a scale of 0-10, people new to stretching should stretch in the 2-3/10 range, specifically feeling a pull in the tight muscle but no pain. Once you are familiar with your own reaction to stretching, you may find you are able to stretch in the 4-6/10 range for more benefit. Muscles need to relax to get fully lengthened. A stretch should last for 30 to 60 seconds. Stretching needs to be done at least once every day. Some people find stretching several times a day keeps them more comfortable and able to move more freely. Set

your personal stretching goal." The class session displays a poster as a reminder with the following: "Stretching should: Be done daily. Not be painful. Be held for a minimum of 30 to 60 seconds." Specifically, per the recommendations for a standardized program (27):

- *intensity* is the "2-3/10 range and eventually the 4-6/10 range" for "a gentle pull but no pain";
- *velocity* is "proceed slowly until you feel a gentle pull";
- *repetitions* are "at least once per day", that is at least one repetition one time per day;
- *duration* is "30-60 seconds",
- *frequency* is "daily".

Options for positioning are also included: lying (elongate, trunk rotation, inner thighs, hip flexors/extensors, hamstrings and quadriceps), sitting (trunk rotation, inner thighs, hamstrings, quadriceps, upper calves and lower calves) and standing (hamstrings, quadriceps, and upper and lower calves).

7) STC demonstrated initial efficacy in a randomized controlled pilot trial.
Ambulatory MS subjects with self-reported spasticity interfering with daily activities were randomized to STC, with two 2-hour group sessions and home practice, or standard of care (SOC) control, with home practice using an illustrated brochure, the National MS Society's *Stretching for People with MS: An Illustrated Manual* (61) without instruction or group support (See Appendix). Subjects completed the self-reported MS Spasticity Scale-88 (MSSS) and examiner-assessed Modified Ashworth Scale (MAS) at baseline and following 4 weeks of either intervention. 40 subjects were randomized and 38 completed both baseline and outcome measurements. Baseline MSSS and MAS scores did not differ between the two groups. Mean MSSS total scores improved more in the STC group than in the SOC control group between baseline and follow-up (STC -27.8, SOC -3.7, $p<0.03$) (Figure 1) and on the MSSS Pain and Discomfort subscale (STC -3.9, SOC +0.3, $p<0.02$) and MSSS Muscle Spasms subscale (STC -5.0, SOC -0.8, $p<0.03$) (Figure 2). Change in MAS did not differ between groups ($p>0.05$). The scores of the other subscales improved more in the STC group than in the SOC group, but not significantly. Additionally, the study found significant improvement in the STC group but not the SOC group in other areas of interest to PwMS: fatigue measured by the Modified Fatigue Impact Scale (STC -6.9, $p<0.031$ and SOC -4.0, $p=0.11$), physical function measured by the MS Impact Scale 29 (STC -6.7, $p<0.003$ and SOC -2.4, $p<0.63$), depression measured by the Beck Depression Inventory II (STC -4.7, $p<0.004$ and SOC -2.27, $p=0.999$) and improved understanding of spasticity and the importance of stretching on a spasticity knowledge test (STC +5%, $p<0.035$ and SOC +2%, $p<0.8$). There were no relapses or serious adverse events during the study. One subject reported a study related adverse event of increased pain from overstretching. He was advised to moderate the intensity and reported no further issues. Subjects were readily recruited and rapidly enrolled. Subjects reported, "I overdid it initially, but now I understand how to stretch without making myself feel worse and actually feel better," and "Thank you for all you do for PwMS and especially this program for spasticity. I

understand spasticity and what my 'triggers' are. Now I can sleep through the night without my legs cramping and waking me up."

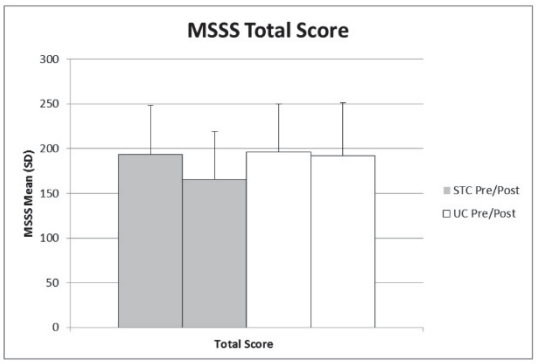

Figure 1

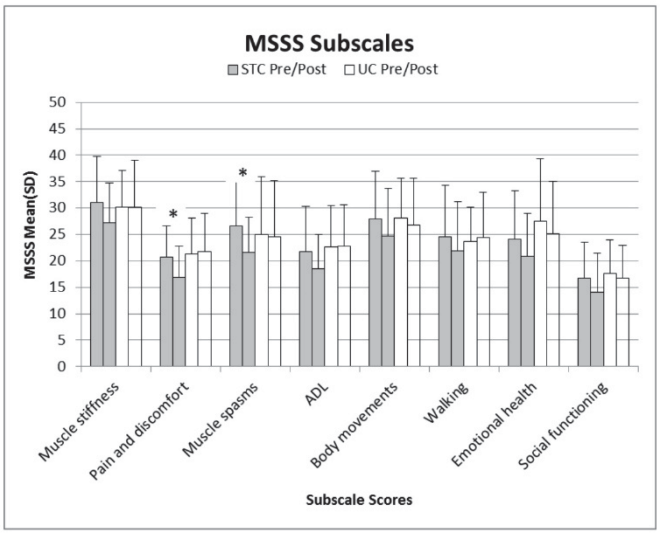

Figure 2

Figures 1 and 2 (above) show means and standard deviations (SD).

The results of the SPiRE pilot study are published in the Multiple Sclerosis Journal: Experimental, Translational and Clinical (DOI 2055217317699993, Sage Publishing). (62) The results were presented as posters at the 6th International Symposium on Gait & Balance in Multiple Sclerosis in 2016 and American Countries on Treatment and Research In MS (ACTRIMS) and American Academy of Neurology (AAN) in 2017.

8) The study has strengths/limitations. Strengths include: significant results on a standardized measure of the impact of MS spasticity compared to control; clinically significant changes in the STC group only on other areas important to PwMS (fatigue, mood and impact on physical components of MS); groups closely matched and representative of the MS population; a very low dropout rate, and no serious adverse events. Limitations include: it was small, at a single location and subjects were followed for only four weeks.

9) Summary After more than 20 years with little progress in the field of understanding and treating spasticity in MS, we are ready to move the field forward. Progress has been stalled due to poor measurement tools to capture the impact and severity of spasticity and poor standardization of the most commonly recommended treatment for spasticity. Now there are standardized measurement tools to capture the impact and severity of spasticity: MSSS and NRS, and a standardized implementation program of the Spasticity Guideline with lower extremity stretching: STC, with demonstrated feasibility and initial efficacy.

C. Research Design and Methods

Overall Experimental Design and Methods:

To address **Specific Aim 1 of the proposed research, to evaluate the STC program on the impact and severity of spasticity and other patient reported outcomes in ambulatory adults with MS and spasticity,** individuals with MS who have self-reported spasticity of the lower limbs will be randomized to receive either comparison program or the STC program. Each arm of treatment will consist of two 2-hour classes, about one week apart. This study will compare the outcomes of STC participants with those receiving comparison program at one month after completing the program. Outcomes will include measures of the impact and severity of spasticity, fatigue, mood, the impact of MS on walking and daily activities, pain intensity and interference and the frequency of participation in stretching for MS lower extremity spasticity in ambulatory adults with MS and spasticity.

To address **Specific Aim 2 of the proposed research, to determine if the effects of STC are sustained for 6 months,** this study will compare the outcomes of STC participants with those receiving comparison program at six months after completing the program.

Sequence of Activities

Schedule of Study Visits

	Consenting Phone Call	Baseline Visit	Class 1^	Class 2^	Outcome Visit 1	Outcome Visit 2
	Up to 2 months before Class 1	Up to 2 months before Class 1	Week 1	Week 2 (1-3 weeks after Week 1	One month after Class 2 (± 2 weeks)	Six months after class 2 (± 1 month)
Consent	X**	X				
Walking measures		X*			X*	X*
Questionnaires		X			X	X
Education and exercise instruction			X	X		
Total time	1 hour	1½ hours	2 hours	2 hours	1½ hours	1½ hours

*If enrolling at VAPORHCS-Portland and live within the Portland metro area and/or are able to come for all 5 activities in persons.

**If enrolling at a location other than VAPORHCS-Portland and/or are not able to do all 5 activities in person.

^Classes will be combined into one 1.5-4 hour session for one-on-one delivery (or small group if randomization and scheduling allows) for participants who are unable to come to VAPORHCS for multiple activities or are unable to do group video conference classes.

Study Activities over the Life of the Study

Months	0-6	6-12	13-18	19-24	25-30	31-36	37-42	43-48
IRB approval	■							
Recruitment cohorts 1-5		■						
Intervention cohorts 1-5			■					
Follow-up cohorts 1-5				■				
Recruitment cohorts 6-10			■					
Intervention cohorts 6-10				■				
Follow-up cohorts 6-10					■			
Recruitment cohorts 11-14				■				
Intervention cohorts 11-14					■			
Follow-up cohorts 11-14						■		
Data entry/Cleaning							■	
Data Analysis/ Report Writing								■

Interventions

To address Specific Aims 1 and 2 of the proposed research, subjects will be randomly assigned to either receive the STC program or a comparison program.

Spasticity Take Control: STC will be delivered in two 2-hour group sessions approximately one week apart and facilitated by a trained member of the study team, the PI or Co-I with assistance from the study coordinator or other qualified research assistant. The first session of STC will be introductions and an optional icebreaker activity, viewing and discussing the education DVD, 10-minute break, viewing and discussing the lower extremity stretching DVD, and preparing for the group stretching session. In the second session, participants will practice all the stretches, and the stretching diary will be introduced. The goal of the second session is to find at least one exercise for each body area for a daily 15-minute stretching routine. Facilitator and participant manuals will be used to guide the program and provide reference material for home use and the stretching exercises. Subjects will be instructed to record their stretching and any falls for six months in their diaries and complete assessments again after one month and six months of home stretching.

Comparison Program: Comparison program will also be delivered in two 2-hour group sessions approximately one week apart and facilitated by a trained member of the study team, the PI or Co-I with assistance from the study coordinator or other qualified research assistant. This program will use the NMSS stretching brochure titled, "Stretching for People with MS: An Illustrated Manual." (61) See Appendix 4. Subjects in this group will also attend two class visits to review the information included in the brochure and to learn the exercises illustrated in the brochure. They will complete the same stretching diary given to the STC group with instructions to stretch daily and record any falls that may occur.

Outcomes

The primary endpoint of the study is after one month of home stretching and the secondary endpoint is after 6-months of home stretching.

1) Multiple Sclerosis Spasticity Scale 88 (MSSS) will be the primary outcome measure of impact of spasticity. See Scientific Rationale A9a above.

2) Numeric Rating Scale for Spasticity (NRS) will be a secondary outcome measure of severity of spasticity. See Scientific Rationale A9b above.

3) Other secondary outcomes will include patient reported measures of fatigue using the Modified Fatigue Impact Scale (MFIS), emotional distress using the PROMIS Depression Short Form v1.0 8a, the impact of MS on walking and daily activities using the Multiple Sclerosis Walking Scale-12 (MSWS-12) and the Multiple Sclerosis Impact Scale-29 (MSIS-29), sleep quality using the Pittsburgh Sleep Quality Index (PSQI),

knowledge of spasticity using a Spasticity Knowledge Questionnaire and pain intensity and interference using a pain questionnaire.

4) Participants will be asked to record time spent stretching and any falls that may occur in an electronic or paper daily diary. More specific information about their stretching participation will be gathered by questionnaires administered by study personnel (Stretching Participation Outcomes questionnaires, versions for NMSS and STC groups). Participants' opinions about the classes and their usefulness will be assessed using a Post-participation Evaluation questionnaire. Participants' opinions about the video teleconference format will be assessed using a Virtual Delivery Evaluation questionnaire.

Whenever possible, questionnaires will be completed online, directly within the REDCap database. However, if a participant prefers paper forms, or has impaired fine motor control and wants to dictate their answers to study personnel (in person or over the telephone), we will offer those options and study personnel will enter the responses into the REDCap database.

5) **Physical measures:**

a) Timed Up and Go (TUG): The time it takes to rise from a chair, walk 10 feet, turn around, and walk back to the chair, turn around, and sit down. The better of two trials will be used.

b) Timed 25 Foot Walk (T25FW): The time to walk 8 meters or 25 feet is strongly related to its ordinal counterpart the Ambulation Index (Spearman r = 0.91), without the variability that the ordinal scale reflects. T25FW will be used in this study to measure ambulation status and as an additional measure of mobility.

Subject Profile

Veterans and others with multiple sclerosis (MS) who are ambulatory with self-reported lower extremity spasticity that interferes with daily activities will be recruited for this study. We need to recruit from outside the VA to get an adequate representation of women in the study. MS is more common in women (3:1) but men with MS are more common in the VA (3:1).

The subjects will meet the following inclusion criteria:

(1) confirmed diagnosis of any subtype of MS
(2) over 18 years of age;
(3) self-reported lower extremity spasticity that interferes with daily activities,
(4) mild-to-moderate MS disability as defined by a PDDS score of < 7, (i.e., be able to walk at least 25 feet with or without an ambulation aid such as a crutch, cane or walker);
(5) fluent in written and spoken English, as materials are not validated in languages other than English
(6) have access to a reliable internet connection and a webcam-equipped device.

The following exclusion criteria will be applied in assessing potential subjects:

(1) self-reported musculoskeletal or neurological condition other than MS that is known to cause spasticity,
(2) any uncontrolled conditions that would preclude reliable participation in the study.

These inclusion and exclusion criteria are minimal requirements for participation in the programs and completion of the patient reported outcome measures.

Statistical Plan and Power Analysis

Based on the pilot data, the mean of percent change for MSSS 88 was -2% for the SOC group and -14% for the STC group. Both had a standard deviation of 0.17. If we believe a 3-fold improvement in percentage change for the STC group vs comparison program group (e.g. 12% decrease in the STC group vs. 4% decrease in the comparison program group) is clinically significant, we will need 100 subjects in each group (200 in total) for achieving 80% power using 2-sided z test at 5% significance level assuming the standard deviation of the percentage change from baseline for all subjects is 0.2. Using 80% power and 10% drop off rate, we will enroll up to 300 subjects total (110 per group).

Univariate statistical analysis will be conducted for all primary and secondary endpoints within each group. For continuous measurements, we will use two-sample t test (for standardized measurements) or Wilcoxon rank sum test to compare the changes from baseline between the two groups, and use paired t test or signed test to determine whether there is a significant change from baseline within each group. For categorical variables, we will use Chi-square test or Fisher's exact test as appropriate for between group comparisons, and McNemar's test for within group comparisons. Weighted Cohen's Kappa will be computed to determine the level of agreement in similar measurements obtained in different approaches from the same patient. A mixed effect model will be used to assess whether the changes over time differ for the two groups. We will use intent to-treat analysis for the comparisons of the two groups throughout. From our experience with web-based questionnaires, we expect a very small number of missing values so we will use complete case analysis in handling any missing information. We will use linear regression models to evaluate the association between the measurements and measurements change from baseline with patient demographic information. Multiple linear regression models may be fitted to compare the measurement changes between two groups if one or more demographic variables need to be controlled.

We will look for correlations at baseline between the self-report and the physical measures. Then we will look for change following program participation. Then we will look at correlations following the interventions.

Inclusion of Women, Minorities, and Children

The Veterans and others recruited for this study will be over age 18. Efforts will be made to include both women and men in this study. Although MS affects more women than men, because the VA provides medical care to substantially more men than

women, based on our prior research with this population we expect that this study will recruit similar numbers of men and women. However, should there be a dissimilar number of men and women recruited, because some studies suggest that spasticity differs between men and women with MS, we will evaluate the effect of gender on outcomes statistically. Efforts will also be made to recruit subjects from minority groups in the same proportion as they are found in the population VISN 20: 78.5% Caucasian 11.7% Latino, 1.8% African-American and 3.7% Asian-American, 0.3% Pacific Islander, 1.4% American Indian/Native Alaskan, and 3.8% reporting two or more races. Children will not be included in this study.

Subject Identification/Recruitment

Subjects will be identified chiefly through pre-screening at the VA MS Clinic using CPRS, or at the OHSU MS Clinic using Epic. We expect to review the records of up to 2000 patients to determine initial eligibility criteria (age, MS diagnosis, presence of spasticity). Veterans will be given preference, as this is a VA-funded study. However, it will be necessary to extend the study to include participants outside the VA to meet study goals and achieve a representative sex ratio.

If patients meet initial eligibility criteria, study staff will approach a potential subject's physician at MS clinic regarding study participation. If the physician agrees that the patient is a good candidate, the physician will inform the patient of the study. If the patient is interested and agrees, the physician will introduce the study coordinator or other qualified study staff. Interested potential subjects will be given a flyer and offered an informed consent form for their reference. The research coordinator or other study staff will describe the study and answer any questions the subject may have at that point. If the subject remains interested, the study coordinator will contact them via telephone after a few days, giving the subject time to familiarize themselves with the material. Potential subjects will be led through a phone screen, which includes an eligibility checklist. Potential subjects that meet the eligibility criteria and state a willingness to participate in the research study will be asked to provide an emergency contact during this phone screening, in case of an emergency during remote classes. If the candidate passes the phone screen, the PI or Co-I will review their medical records to confirm that the candidate meets eligibility criteria. We expect that up to 600 people may complete this process.

We will be sending a recruitment letter to patients that have been seen at the VAPORHCS MS Clinic within the past year. This letter will be sent to patients of VAPORHCS-Portland or a VAPORHCS clinic, and have been pre-screened to determine potential eligibility. Recipients will be asked to reply to the letter, letting the research team know whether they may be contacted by phone regarding this study; the research team may then contact those candidates that have given their express permission to be contacted, and recruitment will proceed as above. The research team may contact recipients to confirm that the letter has been received; this is stated within the letter.

We will also be sending a recruitment letter to patients that have been seen at the OHSU MS clinic. This letter will be sent to patients that have been pre-screened to

determine potential eligibility. OHSU recipients will be sent a flyer along with the letter. Recipients will be asked to reply to the letter, letting the research team know whether they may be contacted by phone regarding this study; the research team may then contact those candidates that have given their express permission to be contacted, and recruitment will proceed as above. The research team may contact recipients to confirm that the letter has been received; this is stated within the letter.

We will also send similar recruitment invitations through MyChart® for potential participants.

Researchers will work with ITG and OCTRI to identify potential participants based upon the above eligibility criteria. Researchers will provide the list of inclusion and exclusion criteria and OCTRI will compile a list of eligible participants. Potential participants will be sent a MyChart® message asking them to participate. There is no risk of duplicate invitations as it is based on MyChart® accounts combined with Epic records and no duplication is possible.

Respondents will see a recruitment message (filed separately for IRB approval with the title "MyChart Recruitment Message") that ends with the invitation question: "Are you interested in this research study opportunity?" They will be able to click Yes or No. If they click Yes, an Epic inbox message will be generated and sent to a study team member coordinator for follow-up with the respondent. If they click No, they will not be contacted.

As with the letters, the research team may contact recipients to confirm the invitation has been received; this is stated within the invitation.

Respondents will also be offered the opportunity to opt-out of future research opportunity messages. Patients who have previously opted out of research opportunity messages through MyChart will not be included in the list of patients to receive the recruitment message and will not be contacted.

Privacy, confidentiality and Data Security: Respondents will be assigned a sequential identification number not containing any identifying information. There is no link to MyChart® or participant identification. All data will be stored in password protected files.

We also plan to make use of Dr. Cameron's Recruitment Repository for MS Projects (IRB #3629). This repository contains names and contact information of people with MS who are interested in further research participation. All subjects included in the repository have consented to being contacted for opportunities for participation in research. The ICF and flyer will be mailed to interested candidates, and recruitment will proceed as above.

We also may make use of the Balance Disorders Laboratory Data Repository for the purpose of recruitment. This is an OHSU repository maintained by Dr. Horak, with names and contact information of past participants of studies at the Balance Disorders Laboratory. We have obtained permission from Dr. Horak to use this repository. All subjects included in the repository have consented to being contacted for opportunities for

participation in research. Initial contact with potential participants will be made by a research assistant who is also a member of Dr. Horak's repository study team.

We also may make use of the Multiple Sclerosis Research Repository for the purpose of recruitment. This is an OHSU repository maintained by Dr. Spain, with names and contact information of people with MS who are interested in further research participation. We have obtained permission from Dr. Spain to use this repository. All subjects included in the repository have consented to being contacted for opportunities for participation in research.

Flyers will be posted at VAPORHCS – Portland and VAPORHCS clinics. They will include a brief description of the procedure, inclusion criteria, information on subjects' time commitment and compensation, and contact information. The flyers may be distributed at community education events including support groups sponsored by the National MS Society. The text of this flyer will also be used on research opportunity websites hosted by the National, regional and local social media platforms utilized by the National MS Society, OHSU, and VHA, including but not limited to, websites, e-mail blasts, newsletters, handouts. Potential subjects will need to contact the study team to express interest in the study

Recruitment will occur on a first-come first-served basis. No eligible potential participant in the United States will be turned away, until the study has closed.

Informed Consent

Once potential subjects have been informed of the study, given the materials, phone screened, and confirmed to have a definite diagnosis of multiple sclerosis and likely to meet other inclusion and exclusion criteria, those who remain interested and plan to attend classes at VAPORHCS – Portland, will be invited to attend a group enrollment and assessment visit. All members of a cohort (made up subjects in both groups for any given session) will attend this visit at the same time; alternate dates will be made available, in the event that the group needs to be split due to size. Subjects may also be scheduled for a one-on-one visit, if unable to make it to the group visit. A presentation describing the study will be given to the group, and then participants will meet individually with a member of the study team to sign the consent form.

Subjects who are unable to attend the enrollment and/or the assessment visits in-person will be mailed the consent form, and will be consented over the phone by a qualified member of the study team. The contents of the consent form will be discussed in full, and the subject will be given the opportunity to ask any questions. The signed consent form will then be sent back to the study team in a pre-addressed, postage-paid VA business reply envelope.

The consent session will be conducted in English. We expect to enroll only native or fluent English-speakers; an inability to follow directions in English is an exclusion criterion, as

several of the assessment tools and the intervention materials used in the study are unavailable in languages other than English.

All enrolled subjects will have the capacity to give informed consent. Being intellectually able to understand and sign an informed consent form is one of the inclusion criteria. It is possible that as many as 300 people will sign a consent form but, because of scheduling conflicts, as few as 220 may actually attend at least one class, and 200 will complete all study procedures.

Risks and Side Effects

The only risks anticipated for the STC and comparison program classes and the functional mobility assessments are minor. Subjects may become fatigued or experience muscle soreness after training or assessments. To guard against fatigue, subjects will be told that they may stop and rest at any time. To guard against muscle soreness, class instructors will teach subjects how to perform exercises to minimize the risk of injury. Subjects may be emotionally distressed, if they are not pleased with their performance on physical assessments, or if they are discouraged by the questions on the questionnaires. Subjects will be told that they may refuse to answer any questions that make them uncomfortable. However, some of the questions about how MS or spasticity affect quality of life are critical for the purposes of the study and must be answered. If someone does not want to answer these kinds of questions, they can choose to not participate in the study. Or, if they choose to answer the questions but they are upsetting, a counselor will be offered to assist with emotional distress, if needed.

The risks to confidentiality are minor. Identifiable data will be kept secure. All paper copies of data will be kept permanently in a locked cabinet in a locked office on VA premises, Building 6, Room 314. On a temporary as needed basis, to facilitate subject recruitment and contact, paper copies also may be kept in the research coordinator, research assistant and intervention facilitators offices in: Building 101, Room 206; Building 100, Room 7D150d; and Building 104, Rooms P5F-131 and P5F-115 in locked cabinets in locked offices. Electronic data will be kept in the OCTRI REDCap database and also in a secure folder on the VA network, accessible only to study staff, in \\R01PORHSM03\Services\Research\ Hugos\STC\. Data may also be kept on VINCI (VA Informatics and Computing Infrastructure), as some data analysis may be performed in VINCI. Data kept in this database will be de-identified.

Participants who attend classes remotely will be asked to do so in a private location alone in their home, to give everyone in the group privacy. However, privacy could be breached if participants are not mindful about it.

There are additional privacy issues using video teleconferencing and we will enable all available encryption and privacy modes when using such apps with our participants and will notify participants ahead of time of the privacy risks these methods may entail.

Risks, both to physical well-being and confidentiality, are very small, and are reasonable in relation to the knowledge expected to be obtained.

Participant Safeguards

This study will be reviewed and approved by the joint VAPORHCS / OHSU IRB before recruitment and enrollment begin. Procedures in this study were specifically designed to minimize risks to the subjects. Personnel leading the STC and comparison program sessions will be qualified to instruct subjects and knowledgeable about working with people with spasticity. The investigators will adhere to the Data and Safety Monitoring Plan described below. Trained study personnel will perform all data collection and information will be coded with a subject identifier to protect subject confidentiality.

Suicidality

We do not expect this population to be potentially suicidal. However, in the event that a subject or potential subject indicates that they are suicidal a "warm transfer" will be conducted, per VA instructions.

Benefits

It is possible but unknown if participants will benefit from the STC or comparison programs. Participants may find that participation the program reduces spasticity or some effects of spasticity. The knowledge gained by this study could contribute to implementation of STC and similar programs in the future, which may benefit others with MS.

Protected Health Information

Subjects' names, addresses, email addresses, and phone numbers will be used for communication with subjects. Birth dates may be viewed during pre-screening in CPRS or Epic to ensure that subjects meet age criteria. Addresses will be needed to mail study materials. Emails will be needed to send online survey link and video teleconferencing. Epic Medical Record Numbers will be accessed and used for identification when screening OHSU patients in Epic. Dates associated with the subject's participation in the study will be recorded on data collection sheets.

Multi-Site Study Concerns

This is a single site study. All classes and outcome visits will be held at either the VAPORHCS main hospital in Portland, at a VAPORHCS clinic, or on a VA-approved video conferencing platform.

Subjects will be pre-screened and recruited from the OHSU MS clinic. The study will use OCTRI REDCap. These are the only components of the study that will be conducted at or through OHSU.

Resources Available

The study will make use of the MS outpatient clinics at VAPORHCS and at OHSU for pre-screening and recruiting potential subjects. This study will also recruit from subject data

obtained from the Recruitment Repository for MS Projects (IRB #3629) maintained by Dr. Cameron, as well as from Dr. Fay Horak's Balance Disorders Laboratory Repository and Dr. Rebecca Spain's Multiple Sclerosis Research Repository (IRB #18541). Consenting, outcome visits, and STC and comparison program class sessions will be conducted in room 201 in Building 101 at VAPORHCS; if this room is unavailable, these study activities may be conducted in the Auditorium in Building 100, Building 101 Room 109, or at NCRAR (Building 104, P5). Attending group classes remotely is available for subjects unable to attend in-person. Data entry and clerical activities will be conducted by the study coordinator at VAPORHCS – Portland, Building 6, Room 314. Paper copies of data will be stored in a locked cabinet in this office. Electronic data will be stored on the VAPORHCS research drive at \\R01PORHSM03\Research\Hugos\STC\, and in an OCTRI REDCap database.

The PI and Co-I expect to be working on concurrent studies throughout the life of this study. Cinda Hugos intends to devote 90-99% of her time to this study, and Dr. Cameron will devote 10% time. It is anticipated that the study coordinator will be 1.0 FTE on this study, and will assist minimally on other studies

Costs To Subjects

None of the participants will pay for any part of the study because all procedures and testing are for research study purposes only. Mobility and quality of life assessments and STC and comparison program training sessions will be free to the study subject.

Subject Compensation

All participants will receive $25 for each of the first three visits (baseline, class 1, class 2) and $50 at each of the two follow-up outcome visits, for a total of $175. This payment is a just compensation for the time taken for participation, but is not large enough to be coercive. The terms of payment are acknowledged in the informed consent form. Payment will be given in the form of Fred Meyer gift cards, if available. If gift cards are not available, compensation will be in the form of electronic funds transfer, check or voucher redeemable at the Cashier window.

Privacy and Confidentiality

All paper copies of data will be kept in locked cabinets in locked offices in Building 6, Room 314, Building 101, Room 206, Building 100, Room7D150d and Building 104, Rooms P5F-131 and P5F-115. Electronic data will be kept in the VA research drive, in \\R01PORHSM03\Services\Research\ Hugos\STC\. Study data will also be stored in an OCTRI REDCap database and will be stored in VINCI for analyses that are performed within VINCI. All VA data will be housed at VAPORHCS at the conclusion of the study, per VA regulations.

Subjects will be assigned a sequential identification number. A master subject list, linking the name of the subject to study ID number, will be kept in a password-protected spreadsheet in \\R01PORHSM03\Services\Research\ Hugos\STC, and will be available

only to members of the study team. The master subject list will be relinquished to VAPORHCS R&D at the close of the study, per VA requirements.

Participants who attend classes remotely will be asked to do so in a private location alone in their home, to give everyone in the group privacy. However, privacy could be breached if participants are not mindful about it.

We will enable all available encryption and privacy modes when using video conferencing apps with our participants and will notify participants ahead of time of the privacy risks these methods may entail.

Information Management

All paper copies of data will be kept at VAPORHCS - Portland, Building 6, Room 314, Building 101, Room 206, Building 100, Room 7D150d and Building 104, Rooms P5F-131 and P5F-115 in locked cabinets in locked offices. Any electronic data will be kept in the VAPORHCS research drive, in \\R01PORHSM03\Services\Research\ Hugos\STC. Study data will be stored in the OCTRI REDCap database.

Subject responses to questionnaires will be transmitted directly to the OCTRI REDCap database as the subjects complete the survey. Data will be exported to the study folder, \\R01PORHSM03\Services\Research\ Hugos\STC\ for data analysis and for long-term storage. Data may also be exported to VINCI in order to perform analyses within the VINCI system. Data shared with OHSU (through the use of REDCap) will be subject responses to questionnaires and date of questionnaire completion; as subjects will be completing the questionnaires on their home computers at the time and date of their choosing, date of questionnaire completion is not the same as date of study visit, and therefore not PHI. Participant names and email addresses will also be stored in the REDCap database, in order that the database may automatically email survey links to participants. This sharing of data is acknowledged in the Informed Consent Form.

Data will be contributed to Dr. Cameron's repository, "Data Repository for Mechanisms of Imbalance and Falls in Multiple Sclerosis" (IRB #2865). Subjects' consent must be obtained before adding their data to the repository; subjects may decline data banking in this repository and still participate in this study. This data will be coded, and a linking key will be kept as an excel spreadsheet in the repository folder, \\R01PORHSM03\Services\Research\Cameron_2865-Repository.

Identifiable data will be contributed to Dr. Cameron's repository, "Recruitment Repository for Multiple Sclerosis Projects" (IRB #3629). This data will not be coded, as it is being retained for recruitment purposes. Subjects' consent must be obtained before adding their data to the repository; subjects may decline data banking in this repository and still participate in this study. Data will be kept in \\R01PORHSM03\Services\Research\Cameron_3629-Recruitment.

Data and Safety Monitoring Plan

Safety monitoring will involve periodic review of adverse events (AEs), dropouts, complaints or breaches of confidentiality. Subjects will be encouraged to report any potential problems at any time to the research coordinator. The safety of the subject will be monitored during the outcome visits and STC or comparison program sessions to ensure the subject is not having any adverse events. Adverse events will be judged by the monitor as related, possibly related or unrelated to the study procedures. Serious adverse events (SAEs), unanticipated problems (UPs) and protocol deviations that are greater than minor will be reported to the VA Institutional Review Board, per VA IRB policy.

Safety data collection will begin with the first report of a problem or potential problem. Safety data will continue to be added as staff becomes aware of safety issues. The PI and research coordinator will review safety data as needed.

The PI and co-I will oversee the safety data. We do not foresee any reasonable conditions that would trigger an immediate suspension of the research.

Step-by-Step Guidance on Conducting the Study

Recruitment

Recruitment will chiefly be conducted through the VAPORHCS and OHSU MS clinics. The research coordinator will use CPRS or Epic to pre-screen potential subjects for the inclusion and exclusion criteria listed above. Once identified, the research coordinator will approach the potential subject's healthcare provider and confirm that the candidate is a good fit. If so, the provider will mention the study to the patient and, if the patient is interested, introduce the research coordinator. The research coordinator will give the candidate a brief overview of the study, as well as the flyer and the informed consent form; the informed consent form is only for the candidate's reference, and will not be signed or collected at this point. The research coordinator will answer any questions the candidate may have about the research, and will request permission to make a follow-up telephone call the following week. After giving the potential subject about a week to consider participation, the research coordinator will follow up with a phone call, using an IRB-approved telephone screening script. If the candidate remains interested, the screening questionnaire will be conducted. If the candidate passes the screen, and is a patient at the VA or OHSU, the PI will review the candidate's medical records to ensure potential eligibility. Once the PI approves the candidate for study participation, he/she may be scheduled for an enrollment visit.

Due to the COVID-19 pandemic, we may restrict in-person clinic recruitment to comply with social distancing guidelines. The study staff may continue to screen upcoming visits in Epic and CPRS; these may be telehealth clinic visits or in-person clinic visits. Study staff may alert providers to any promising candidates that are scheduled for clinic visits and ask the provider to mention the study to the patient. If the patient is interested,

the provider may ask the patient if they may give their permission to be contacted by study staff. If the patient agrees, the provider will inform the study staff, who may then contact the study candidate. Recruitment then proceeds as above.

We will also be mailing IRB-approved recruitment letters to patients who have been seen at the VAPORHCS MS Clinic and the OHSU MS Clinic in the past year. These patients will be pre-screened to determine potential eligibility before the letter is sent; this is in accordance with the study's OHSU HIPAA Waiver and with the VAPORHCS Waiver of Authorization for Screening/Recruitment purposes. This letter will inform recipients of the study, and request permission to contact recipients regarding the study. The research coordinator will not be permitted to speak with recipients about the study without first receiving their express permission via a return letter. The research coordinator may contact the recipient to confirm that the letter was received.

Some candidates may be found by using the Recruitment Repository for Multiple Sclerosis Projects (IRB #3629) maintained by Dr. Cameron, as well as Dr. Fay Horak's Balance Disorders Laboratory Data Repository and Dr. Rebecca Spain's Multiple Sclerosis Research Repository (IRB #18541). The records included in these repositories will be pre-screened for potential eligibility; likely candidates will be contacted by telephone by the research coordinator and informed of the study. Individuals identified from Dr. Horak's repository will be contacted by a member of the study team who is also a member of Dr. Horak's repository team, per the SOP of that repository. Interested candidates will be pre-screened as described above, and potentially scheduled for an enrollment visit. Individuals identified from and Dr. Rebecca Spain's Multiple Sclerosis Research Repository will be contacted by a member of the study team who is also a member of Dr. Spain's repository team, per the SOP of that repository. Interested candidates will be pre-screened as described above, and potentially scheduled for an enrollment visit.

Initial contact may also occur by telephone, if a potential subject contacts the study team about this study after learning about it in the community, e.g. by reading an IRB approved flyer or seeing the flyer text on a recruitment website. In this event, the research coordinator will conduct the telephone screening questionnaire. If candidate proves likely to be eligible, the study materials mentioned above will be mailed to the candidate, including the ROI if necessary (see below); pre-screening and scheduling will proceed as described above.

If the candidate is not a VA or OHSU patient, he/she will be required to provide a copy of their most recent Multiple Sclerosis progress notes to confirm diagnosis of MS and pre-screen for any potential exclusions. The research coordinator may mail the subject a copy of the facility-specific Release of Information Form used by the candidate's health care facility. Full medical records will not be requested, but only the most recent MS chart notes. Once chart notes are received from the candidate's health care facility, the PI will confirm likely eligibility, and the candidate may be scheduled for an enrollment visit.

Once subjects have agreed to participate, they will receive reminder calls before every future study visit or study activity, such as receiving the link to the online questionnaires, 1-2 working days before that visit/activity. Subjects who agree to participate remotely (See Alternative Delivery Format) will be asked to join a one-on-one video call 1-2 working days before the first study visit where a study staff member will assist with webcam set-up if needed, confirm emergency contact information, and review the functionality of the online platform.

Baseline Visit – VAPORHCS-Portland Participants

Subjects who plan to participate at VAPORHCS-Portland and are able to attend all 5 visits will be invited to a group baseline visit. All potential members of a cohort will be invited. Multiple visits may be scheduled, as it may be necessary to divide the visit due to size of a cohort. An individual enrollment visit may be scheduled, if a participant is unable to come in on the scheduled date for a group visit. This visit will be conducted in VAPORHCS Building 101, room 201. In the event that this room is unavailable, this visit may be conducted in the Auditorium in Building 100, in 7D153, or in NCRAR. All candidates will have been given an Informed Consent Form for review prior to this visit. The PI or another qualified member of the study team will give a group presentation and consenting discussion on the study, and the candidates will have the opportunity to ask questions.

Qualified members of the study team will be available to assist the candidates with completing the consent forms. Candidates will meet with a study team member individually to sign the consent forms. Consent will involve agreement to participate in all components of the study and agreement to randomization into one of the two study arms. The HIPAA Authorization Form will be discussed and signed as well. All potential subjects who meet the inclusion and exclusion criteria, consent to participate, and provide authorization for the use of their results will be invited to enroll.

There will be a sufficient number of study staff available to administer the following mobility assessments to up to 30 participants; these activities may not be performed until a participant has signed the consent and HIPAA forms.

Timed Up and Go (TUG): Subject will begin this test seated in a firm chair. They will be timed getting up from the chair, walking 10 feet to a pre-marked line on the ground, turning around, walking back to the chair, and sitting back down. Subject will be instructed to do this at a normal, comfortable walking speed. This assessment will be performed twice, with the faster of the two times used in analysis.

Timed 25-Foot Walk (T25FW): Subject will be timed walking on a pre-measured course of 25 feet. Subject will be instructed to do this as quickly but safely as they are able. This assessment will be performed twice, with the faster of the two times used in analysis.

All walking assessments may be performed using the subject's preferred assistive device, if any. Assistive device use will be recorded on the data collection sheet, so that we may request that subjects are consistent with device use at outcome visits.

Once walking assessments are completed, subjects will be dismissed. They will be told that they will be emailed a link to the following online questionnaires, to be completed from their home computer or other computer of their choice:

Spasticity Knowledge Questionnaire will be taken to establish baseline knowledge of spasticity.

Demographics and Medical History and the Patient Determined Disease Steps (PDDS) will be collected to describe the study population. The PDDS is a self-report measure of walking mobility using an ordinal scale of 0 (Normal) through 8 (Bedridden). It was developed as an inexpensive surrogate for the Expanded Disability Status Scale (EDSS) and scores from the PDDS are linearly and strongly related with physician-administered EDSS scores (r = .93). **Disease Course** will be self-reported using graphical figures.

MS Spasticity Scale 88 (MSSS) asks about spasticity symptoms and the impact these symptoms have on daily life.

Numeric Rating Scale for Spasticity asks about severity of spasticity, on a scale of 0-10.

PROMIS Depression Short Form v1.0 8a is an 8-question self-report questionnaire for measuring the severity of depression and emotional distress.

Modified Fatigue Impact Scale (MFIS) is a 21-item questionnaire to evaluate the impact of fatigue on physical, cognitive, and psychosocial functioning in people with MS.

Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item questionnaire that is a recommended outcome measure for quality of life in exercise studies in people with MS.

Multiple Sclerosis Walking Scale (MSWS-12) is a 12-item validated self-report questionnaire that assesses the subject's perception of the impact of MS on their walking.

Pittsburgh Sleep Quality Index (PSQI) is 19 item self-report questionnaire that assesses sleep quality over the past month.

Pain Questionnaire (adapted from the validated Brief Pain Inventory – Short form) asks about the presence of pain and whether it is chronic (>3 months duration), includes body part descriptions to identify extent of pain, four questions about pain intensity and seven questions about pain interference in the past 24 hours.

Virtual Delivery Evaluation is a 14-item questionnaire that asks participants about their satisfaction using the VA-approved video teleconference delivery format.

Subjects also will be asked to report all medications used to manage spasticity as well as medications for multiple sclerosis management and walking or gait difficulties.

Finally, the baseline questionnaires will include questions about all the ways patients currently manage their spasticity (Pre-participation Questionnaire).

Subjects will be told that they can be taken to the VAPORHCS library to complete these questionnaires, if it is difficult for them to access a computer. These questionnaires may also be completed over the phone with a member of the study team, if desired. Paper questionnaires may be given to subjects instead of the computer questionnaires, if needed. Subjects will be asked to complete the questionnaires by a certain date, about a week after their visit. They will be told that they will not be able to be randomized to a class group until these questionnaires have been completed. Subjects may be called by the study team after completing questionnaires to clarify any information needed.

If we are unable to copy them at the time they are signed, subjects will be told that a copy of their signed consent form and HIPAA authorization will be mailed to them. They will be told that once they complete their questionnaires, they will be informed of their class assignment and schedule.

Once a participant has completed their baseline visit and questionnaires they will be randomly assigned to one of the two treatment groups, stratified by gender. We will use the randomization module in REDCap to randomize males and females separately in blocks whose sizes are randomized to 2 or 4. This strategy will increase the likelihood of gender balance and allow for smaller cohort sizes while preserving the integrity of the blind.

Phone Consent and Baseline Measures

Subjects who are unable to attend an in-person baseline assessment will be consented over the phone by a qualified member of the study team. We will obtain written informed consent and authorization for the study, however, we are requesting a waiver of documentation of consent/authorization so that the subjects may complete the baseline questionnaires *before* the study team receives the signed consent/authorization forms.

The ICF, HIPAA, NOPP and NOPP acknowledgment forms, baseline questionnaires and two VA business reply envelopes will be sent to potential participants in preparation for phone consenting. A study team member will arrange a time for the phone consent with the potential participant. After completing the consent process with a study team member, and while still on the phone, the potential participant will sign/date/time as needed, to ICF, HIPAA and NOPP forms and place them in one of the pre-addressed, postage-paid VA envelopes. After the phone call is concluded, the (now) participant will complete the baseline questionnaires. The questionnaires have no identifiers other than a coded subject ID number and will be

returned separately from the consent form in the other pre-addressed, postage paid VA business reply envelope as soon they are completed. If the participant prefers to complete the baseline questionnaires online, a link to the REDCap survey will be emailed to them. Randomization will proceed as usual following receipt of the consent form and baseline questionnaires. A copy of the signed ICF, HIPAA and NOPP forms will be mailed to the participant.

Participants may take the timed walking tests before the first class session if they were not completed as part of the baseline visit.

Spasticity Take Control Classes

Approximately half of the participants will be randomized to receive the STC program. STC will be delivered in two 2-hour group sessions approximately one week apart, and will be facilitated by a trained member of the study team, the PI or co-I, with or without assistance from another member of the study team. Spasticity Take Control classes will be offered as in-person small groups at the VAPORHCS Portland Hospital or a CBOC clinic, or through a VA-approved video conferencing platform.

The first session will take place no more than 2 months after the date of consent. This session will consist of introductions and an optional icebreaker activity, viewing and discussing the education DVD, a 10-minute break, viewing and discussing the lower extremity stretching DVD, and preparing for the group stretching session. In the second session, participants will practice all the stretches and the stretching diary will be introduced. Participants will be provided written instructions for completing the diaries. The goal of the second session is for each participant to find at least one exercise for each body area for a daily 15-minute stretching routine. Facilitator and participant manuals will be used to guide the program and provide reference material for home use and the stretching exercises. For more information, see Preliminary Studies sections 5 and 6, above.

Comparison Program Classes

Approximately half of the participants will be randomized to receive the comparison program. The comparison program will be delivered in two 2-hour group sessions approximately one week apart, and will be facilitated by a trained member of the study team, the PI or co-I, with or without assistance from another member of the study team. This program will use the National MS Society stretching brochure, titled “Stretching for People with MS: An Illustrated Manual.” Comparison program classes will be offered as in-person small groups at the VAPORHCS Portland Hospital or a CBOC clinic, or through a VA-approved video conferencing platform.

The first session will take place no more than 2 months after the date of consent. This session will consist of introductions and an optional icebreaker activity, reviewing the information included in the brochure, learning the exercises illustrated in the brochure, and

preparing for the group exercise session. In the second session, participants will practice all the exercises and the stretching diary will be introduced. Participants will be provided written instructions for completing the diaries.

Alternative delivery format:

Classes will be offered as in-person small groups at the VAPORHCS Portland Hospital or a CBOC clinic, or through a VA-approved video conferencing platform. To participate via video conferencing, participants will need to have a reliable internet connection, equipment (computer, tablet, or phone) with video conferencing capability and have privacy in their house for the group session. People who cannot attend in-person group classes or who do not have video conferencing capability or a private space at home will be offered the classes as described or given the option of one 1.5-4 hour session for one-on-one delivery, in person or via video conferencing. Our same trained facilitators will deliver the one-on-one intervention.

Outcome Visit One

Participants will be sent a link to the questionnaires for completion. This visit will occur about one month after the second class session. Participants who had classes at VAPORHCS and can attend the one month, in-person group follow-up assessment will gather as a group to perform the walking assessments. Those who are unable to make it to the group visit may be scheduled for a one-on-one visit, at the discretion of the research team. Alternate group visits may also be scheduled. As these assessments are very quick, participant arrival will be staggered in 15-minute blocks. For example, 3-6 participants may be told to arrive on the hour, 3-6 more may be told to arrive at quarter after, etc. The research coordinator or other member of the study team will welcome participants, and ask about any adverse events that may have occurred since the last visit. The TUG and T25FW measures will be administered by assessors who are blinded to group assignment. Questionnaires completed by subjects will consist of all questionnaires used at the baseline visit, excluding the PDDS, Pre-participation and Demographics and Medical History questionnaires, and adding the Post-participation Evaluation questionnaire. Information that will be collected directly (in person or by telephone) from subjects by study personnel at the time of outcome visit 1 will include changes since baseline in medications taken for spasticity, MS or walking/gait difficulties. In particular, we will ask about adding and dropping any medications from those reported at baseline, as well as increases or decreases in amounts of spasticity medications taken from those reported at baseline. Study personnel also will ask directly about subjects' stretching participation (Stretching Participation Questionnaire: NMSS or STC version, depending on their random group assignment). Participants will be compensated as outlined in the informed consent, and told that the next visit will be in about 5 months.

Participants who had classes at an outlying clinic and cannot attend the in-person group assessment will not complete walking assessments. They will be emailed a link to the questionnaires and will provide information about medication changes and stretching

participation by telephone. These participants will receive the same reimbursement as those who completed walking assessments. Payment will be mailed to these participants.

Outcome Visit Two

Participants will be sent a link to the questionnaires for completion. This visit will occur about six months after the second class session. Participants who had classes at VAPORHCS and can attend the six month, in-person group follow-up assessment will gather as a group to perform the walking assessments. Those who are unable to make it to the group visit may be scheduled for a one-on-one visit, at the discretion of the research team. Alternate group visits may also be scheduled. As these assessments are very quick, participant arrival will be staggered in 15-minute blocks. For example, 3-6 participants may be told to arrive on the hour, 3-6 more may be told to arrive at quarter after, etc. The research coordinator or other member of the study team will welcome participants and ask about any adverse events that may have occurred since the last visit. The TUG and T25FW measures will be administered by assessors who are blinded to group assignment. With the exception of the Spasticity Knowledge and Post-participation Evaluation Questionnaires, all of the questionnaires and information collected at Outcome Visit One will be collected at Outcome Visit Two. Subjects still active in the study will be asked to complete the Pain Questionnaire twice: once as if they were answering it prior to participation in the current study and the second time answering it as they are about to exit the current study. Participants will be compensated as outlined in the informed consent for their time.

Participants who had classes at an outlying clinic and cannot attend the in-person group assessment will not have to complete walking assessments. They will be emailed a link to the questionnaires and will provide information about medication changes and stretching participation by telephone. These participants will receive the same reimbursement as those who completed walking assessments. Payment will be mailed to these participants, along with the materials for the class that they did not receive.

If participants have not returned their diaries on schedule, they will receive reminder calls or a letter. A variation of the letter will be sent with future diary pages encouraging participants to continue diary completion during the study.

Data Entry and Maintenance

The study coordinator will maintain the original hard copies of all data generated from study visits. This data will be kept in cohort-specific binders, each labeled with the study ID numbers included in the cohort, kept in a locked cabinet in a locked office, Building 6, Room 314. Also included within these binders will be the signed informed consent and HIPAA authorization forms, completed phone screens, and ROI and medical records obtained from subject's healthcare provider, for subjects that are not VAPORHCS or OHSU patients.

Class attendance will be recorded by the program facilitator on a sign-in sheet at each class. This sheet will be given to the research coordinator, and will be kept in a binder or

folder dedicated to class attendance, which will be kept in a locked cabinet in Building 6, Room 314. Attendance data will be transferred into a spreadsheet, which will be maintained in \\R01PORHSM03\Services\Research\ Hugos\STC.

Online questionnaires will be entered directly into REDCap by the subject. This data will be exported to \\R01PORHSM03\Services\Research\ Hugos\STC and may be exported to VINCI, as some analyses may be performed in VINCI. Data from participants who prefer paper questionnaires, and all other data recorded on paper, such as physical assessments, stretching participation, and medication changes, will be entered by a member of the study team into REDCap.

Assessment of Outcomes

The primary outcome for Specific Aim 1 will be the difference in the change in impact and severity of spasticity and other patient-reported outcomes for STC and the comparison program subjects at one month post-intervention. The short-term impact of the interventions on spasticity and other patient-reported outcomes will be determined by comparing changes in mean questionnaire scores from the baseline visit to the first outcome visit.

Univariate statistical analysis will be conducted for all primary and secondary endpoints within each group. For more information, see “Statistical Plan and Power Analysis,” above.

The primary outcome for Specific Aim 2 will be the difference in the change in impact and severity of spasticity and other patient-reported outcomes for STC and the comparison program subjects at six months post-intervention. The long-term impact of the interventions on spasticity and other patient-reported outcomes will be determined by comparing changes in mean questionnaire scores from the baseline visit to the second outcome visit.

Alternate Approaches Should Proposed Methods Fail

In the event recruitment proves more difficult than anticipated or we cannot rely on support from the NMSS, we will advertise the study in local media. This change has been reflected in the budget justification.

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Appendix

All supporting documents have been uploaded to the eIRB.