Study Protocol

Qigong for Multiple Sclerosis: A Feasibility Study

NUNM IRB#: 102015

10-6-2016

Title of Study: Qigong for Multiple Sclerosis: A Feasibility Study

Principal Investigator: Dr. Angela Senders, ND, MCR (503) 552-1743

Student Investigator: Lita Buttolph, PhD (503) 552-1886

Clinical Investigator: Dr. Paul Kalnins, ND, MSOM (503) 552-1551 ext. 1774

IRB#: 102015

Version#: 10-06-16

Document Approval Date: 10/06/16

ABSTRACT

Background: Multiple Sclerosis (MS) is a chronic, autoimmune disease of the central nervous system that affects over 2.3 million people worldwide.[1] People with MS can experience a variety of symptoms, including impaired motor function and balance, fatigue, pain, impaired cognition, and depression. Ancient Chinese movement arts, such as taiji and qigong, have been shown to improve quality of life, balance and fatigue in a variety of chronic conditions.[2–8] However, very little published research has been conducted on the effect of these practices specifically for people with MS.[9]

Objective: The primary goal of this study is to assess the feasibility of weekly community qigong classes for people with MS. A secondary goal is to test the effect of weekly community qigong classes on quality of life, balance, and gait for people with MS.

Participants and Design: In this non-blinded randomized controlled feasibility trial, twenty adults with any type of MS will be randomized to either a qigong intervention (n=10) or wait-list control group (n=10). The intervention group will participate in 60-to-90 minute community qigong classes once a week for 10 weeks. Participants will choose from four vetted qigong instructors and will select a class that is geographically convenient and fits their schedule. This pragmatic design maximizes external validity by reflecting the ways in which people with MS initiate qigong practice in the real world. Feasibility outcomes include recruitment, adherence to the qigong intervention, and ability to participate. Secondary outcomes include validated measures of quality of life (PROMIS, the Multiple Sclerosis Impact Scale), balance (the Four

Square Step Test), gait (the MS Walking Scale, Timed 25-Foot Walk Test, and Timed-up and Go), and fatigue (PROMIS, Modified Fatigue Impact Scale) collected at baseline and 10 weeks.

Results from this trial will provide preliminary data to seek future funding for a fully powered randomized controlled trial of qigong and MS.

A. SPECIFIC AIMS

Aim 1: To assess the feasibility of weekly community qigong classes for people with any type of MS. Specific feasibility outcomes include (1) ability to recruit and enroll participants with MS; (2) adherence to the intervention protocol as measured by class attendance and home practice; and (3) ability of participants to take part in qigong exercises.

Aim 2: Assess the ability of weekly community qigong classes (n=10) compared to wait-list control (n=10) to improve balance, mobility, quality of life, and fatigue for people with MS. Validated outcome measures will be administered at baseline and immediately post-intervention and include quality of life (PROMIS, the Multiple Sclerosis Impact Scale), balance (the Four Square Step Test), gait (the MS Walking Scale, Timed 25-Foot Walk Test, and Timed-up and Go), and fatigue (PROMIS, Fatigue Severity Scale).

Because this is a small feasibility study, the data collected are meant to be hypothesis-generating. Any clinically meaningful trends toward improvement will justify further exploration of qigong for MS.

B. BACKGROUND AND SIGNIFICANCE

Multiple Sclerosis (MS) is a chronic, autoimmune disorder affecting the central nervous system.[1] The National MS Society estimates that 2.3 million people globally have MS.[1] The National Institute for Health estimates that 250,000 to 350,000 people are diagnosed with the disease in the US, with an estimated 200 new cases each week.[10] Medications have been shown to slow the progression of the disease and help manage symptoms, although they often come with adverse side effects ranging from mild to severe (e.g., nausea, vomiting, hemorrhagic cystitis, and cancers).[11,12]

B.1. SYMPTOMS AND DISEASE STAGES

Multiple Sclerosis results in damage to the myelin sheath and nerve fibers of the central nervous system (CNS). Symptoms vary depending on where in the CNS the damage occurs. Some of the

most common symptoms of MS include vision problems, muscle weakness, gait dysfunction, poor balance, numbness and/or prickling sensations, bowel and bladder dysfunction, fatigue, dizziness, vertigo, sexual dysfunction, pain, depression, decreased memory, and decreased cognitive ability.[13]

There are currently four identified courses of MS, each of which may appear in mild to severe form. These include (1) Relapsing-Remitting; (2) Primary-Progressive; (3) Secondary-Progressive; and (4) Progressive-Relapsing MS (Table 1).

Table 1. Courses of MS[1]

Course of MS	Characteristics	% of People with MS
Relapsing-Remitting (RR-MS)	Alternating attacks or "flare-ups" of neurologic symptoms followed by periods of remission	85% initially receive this diagnosis
Primary-Progressive (PP-MS)	Steady, slow worsening of neurologic function from onset with no remission	10% initially receive this diagnosis
Secondary-Progressive (SP-MS)	Steady, slow worsening of neurologic function with no remission after an initial relapsing-remitting period	50% of those with RR-MS develop SP-MS after 10 years.
Progressive-Relapsing (PR-MS)	Steady, slow worsening of neurologic function with no remission mixed with episodes of more intense "flare-ups"	5% initially receive this diagnosis

B.2. EXERCISE AND MS

Many clinical trials have investigated the relationship between MS and exercise.[14–22] A recent systematic review by Latimer-Cheung and others found that people with mild-to-moderate disability from MS who engaged in moderate-intensity exercise two times per week benefitted from increased aerobic capacity and muscular strength.[19] The authors also found that exercise may improve mobility, fatigue, and health-related quality of life for people with MS.[19] Mayo et al. recommend that exercise programs for people with MS be "interesting, relevant to the individual, and easily implemented across a variety of settings."[21, (p. 2)] When comparing people with MS to people without MS, they found that "people with MS expressed the need to feel safe and have clear professional instructions provided on proper techniques, intensity and duration ."[21, (p.2)] These findings suggest that exercise programs that are instructor-led, of

moderate intensity, allow adjustments to individual needs and restrictions, and are intellectually stimulating may be well-suited for people with MS.

B.3. QIGONG

Qigong is an ancient Chinese movement art developed to promote health, longevity and well-being. Qigong exercises often involve a combination of gentle movements, meditation, breath-work and visualization. Taiji (also known as tai chi or tai chi chuan), is similar to qigong but includes a martial art/self-defense component. Taiji has been described as a "complex multi-component intervention integrating neuro-musculoskeletal training, breathing, and various cognitive strategies (e.g. imagery, focused attention), often embedded within a rich psychosocial framework"[23 (p.4)] Both taiji and qigong are mind-body exercises commonly taught in structured classes. Both are growing in popularity due to their reported health benefits, safety and low cost.

A number of scientific studies have documented the health benefits of qigong and taiji. Several clinical trials of qigong and/or taiji have found significant improvements in balance and gait,[2,4,5,24,25] fatigue,[6,7,8,26] and quality of life.[8] Several studies of Parkinson's disease found beneficial effects from taiji and/or qigong, including improved balance, mobility, sleep, health-related quality of life as well as reduced pain.[3–5] Other studies have looked at the effects of qigong on fatigue, anxiety and depression in people with Chronic Fatigue Syndrome (CFS), showing improvements in these symptoms as a result of qigong practice, along with improved mental functioning and telomerase activity.[6,7] Two recent studies evaluated the effects of qigong on pain reduction for people with fibromyalgia, finding significant improvements in pain, psychological health, and physical function [27,28]

Despite the number of studies looking at the effects of qigong and taiji on neurological disorders, there has been very little published research on the effects of qigong and MS. One pilot study, using a sample of 16 people with secondary progressive MS, found statistically significant improvements in depression and balance after two-months of one-on-one mindfulness taiji/qigong sessions (a total of 6 sessions).[29] Despite the promising findings of this study, the non-validated symptom rating questionnaire limit its generalizability to a broader population. The potentially high cost of one-on-one training sessions may also limit its applicability in the real world.

C. RESEARCH DESIGN AND METHODS

C.1. EXPERIMENTAL DESIGN

The proposed randomized controlled pilot study will assess the feasibility for people diagnosed with MS (n=20) to attend community qigong classes once a week for 10 weeks. The primary goal is to determine the feasibility of the study process (i.e., recruitment, retention, adherence, and pragmatic design). The secondary aim is to assess effectiveness of qigong for people with MS, specifically looking at quality of life, balance, gait performance and fatigue. Potential participants will undergo an initial telephone screening for eligibility, followed by an in-person visit in which they will review and sign an informed consent form, complete a demographic survey, complete the Timed-25-Foot-Walk Test to verify eligibility, and complete baseline outcome surveys and tests. Eligible participants will be randomly assigned to the qigong intervention group or a wait-list control group. The qigong group will be asked to attend 60 to 90 minute long pre-vetted qigong classes once a week for 10 weeks and encouraged to practice daily at home. Criteria for selecting qigong classes are described in more detail below. To track adherence, participants will have an attendance card that they check at each class. Qigong instructors will also keep track of attendance of all study participants.

Those assigned to the control group will be asked to refrain from qigong, taiji or yoga during the 10-week trial period. Following the collection of outcome measures after 10 weeks, the control group participants will be given the opportunity to participate in a subsequent 10-week qigong intervention. Outcome measures will again be collected immediately after the 10-weeks of qigong for the wait-listed control group.

We chose a pragmatic design to enable participants to 1) select an instructor and qigong style they prefer, 2) select a class that fits their schedule, 3) select a class location that is geographically accessible, and 4) immediately begin the qigong intervention without waiting for other participants to be recruited. We expect these pragmatic benefits to help with recruitment and retention of participants. Furthermore, this trial design maximizes external validity by reflecting the way people with MS are referred to or encounter qigong in the real world.

C.2. SCREENING AND STUDY ACTIVITIES

All study visits will take place at the National University of Natural Medicine (NUNM) Helfgott Research Institute, excluding qigong class, which will occur in separate locations throughout Portland.

C.2.1. TELEPHONE SCREENING

Potential participants will be screened over the phone by the student investigator prior to scheduling the first visit. A standardized telephone script will be used to describe the study and determine eligibility. (See Attachment 2 for copy of telephone script). If the potential participant meets the initial eligibility criteria and agrees to be in the study, he/she will be assigned a study ID number and scheduled for Visit 1. A copy of the consent form will be emailed or mailed to the participant for their review at least 24 hours prior to Visit 1. A list of pre-vetted qigong classes and instructors will also be mailed or emailed to participants prior to Visit 1. This list will include a description of each qigong style and brief biography of each instructor.

C.2.2. *STUDY ACTIVITIES*

Study Visit 1: Screening and Baseline (Week 1 of the study)

This study visit will take about 90 minutes. Participants will be asked to do the following:

- Review and sign consent form.
- Complete the Timed-25-Foot-Walk Test (T25-FW) to verify eligibility (i.e., ability to walk 50 feet without assistive devices).
- If participants are able to complete the complete T25-FW they will be asked to complete the Four Square Step Test, and the Timed-Up and Go.
- Complete a demographic/physical activity/treatments/medications questionnaire to determine baseline conditions and potential covariates.
- Complete medications log to document all medications/supplements that participant is currently taking.
- Complete on-line surveys.
- The study coordinator will review the list of qigong classes and instructors with the participant, and answer any questions he/she may have about the pre-vetted classes. Based on this discussion, participants will be asked to select a class they wish to attend if they are selected to be in the intervention group.

Following Study Visit 1, participants will be randomly assigned to the qigong intervention or control group by a pre-established randomization scheme with a block size of four. Some qigong classes may not be available to join immediately, depending on the class schedule and number of participants already attending the class. Thus “Week 2” may not actually begin one week following Visit 1, but will begin once the chosen qigong class is able to accept the participant

into the class. The potential delay from Visit 1 to beginning of the intervention period may range from one week to up to 2 months. We will make every effort to time the screening process in a way that minimizes wait times for participants.

Weeks 2-11 of the study

- Participants assigned to the qigong group will attend one pre-vetted 60-90 minute community class per week for 10 weeks, and will be encouraged to practice at home.
- The wait list control group will continue usual activities and care while refraining from any qigong, tai chi or yoga.

Study Visit 2 (Week 12 of the study)

This study visit will take about 60-90 minutes. Participants will be asked to do the following:

- Repeat the surveys completed at Visit 1.
- Repeat the three physical tests completed at Visit 1.
- Complete medication log follow-up to determine if there have been changes to medications/supplements since baseline.
- Complete an exit questionnaire for those in the qigong group.
- Wait-list control group members will be invited to join a new qigong group and participate in 10 weeks of qigong classes.
- Wait list control group members who choose not to join the qigong group will be asked to complete an exit questionnaire at this visit.

Study Visit 3 (Week 23 of the study – only for control group participants that continue with qigong)

This study visit will take about 60-90 minutes. Participants will be asked to do the following:

- Repeat the surveys completed at Visit 1.
- Repeat three physical tests completed at Visit 1.
- Complete medication log follow-up to determine if medications have changed since Visit 1 and 2.
- Complete an exit questionnaire.

Table 2. Study related activities.

	Visit 1 – everyone	Qigong group only*	Visit 2 - everyone	Qigong for control group only*	Visit 3 – control group only
Week #:	1	2-11	12	13-22	23
Review consent form and sign if agree	X				
Complete demographic/physical activity/treatments/medications questionnaire	X				
Complete medications log	X		X		X
Complete online surveys	X		X		X
Complete physical tests	X		X		X
Attend qigong classes (once/week)		X		X	
Log home qigong practice		X		X	
Complete exit questionnaire			X		X
Expected visit length (hours)	1 – 1.5		1 – 1.5		1 – 1.5

*Investigator will call to check-in on participant status weeks 1, 2 and 7 of the intervention.

C.3. PARTICIPANT RECRUITMENT

Recruitment will begin only after NUNM Institutional Review Board approval has been obtained. Prospective study participants will be recruited from the greater Portland Metropolitan Area, including NUNM Teaching Clinics, the Oregon Health & Science University (OHSU) Multiple Sclerosis Center, the MS Society – Oregon Chapter, and the community at large. Dr. Senders has a joint appointment at NUNM Helfgott Research and OHSU, thus facilitating collaborative arrangements between the two institutions. A draft of the proposed design has already been presented to neurologists at the OHSU MS Center and they have agreed to discuss this study with patients they think would be good candidates. We will send an email announcement through the MS Society Oregon Chapter, which has a mailing list of approximately 7500 members. We will give a presentation to the NUNM clinical faculty about

this study to recruit patients from NUNM clinicians. The NUNM EPIC site specialist identified 40 people with MS seen at the NUNM Clinics between November 1, 2011 and November 1, 2014. A waiver of HIPAA authorization will be submitted to allow us to contact these patients and notify them of this study. Flyers about this study will be posted at NUNM, OHSU, and the qigong studios selected for this study. We will also invite qigong instructors selected for this study to announce this study to their classes and/or patients to help recruit participants. All recruitment materials will be approved by the NUNM Institutional Review Board.

C.3.1. INCLUSION CRITERIA

- Adults, age 18 and older
- Self-reported diagnosis of any type of MS
- Ability to walk 50 ft. without assistive devices (self-report during phone screen and objective demonstration at screening visit using the Timed-25-Foot-Walk Test)
- At least 3 months stable on disease-modifying medication
- Willingness to participate in qigong exercises for the duration of the study if selected in the intervention group
- Willingness to avoid qigong, taiji or yoga for the duration of the study if selected for the control group

C.3.2. EXCLUSION CRITERIA

- Pregnant or nursing women
- Self-reported physical or mental illnesses that would prevent attendance and participation in qigong exercise
- Any regular qigong, taiji or yoga practice occurring once a month or more within the past 6 months
- MS relapse in the 30 days prior to baseline

C.4. QIGONG INSTRUCTOR RECRUITMENT

Experienced qigong instructors will be recruited for this study based on inclusion/exclusion criteria listed below.

C.4.1. INCLUSION CRITERIA

- Five years or more qigong instruction experience (including assistant teaching)
- Experience teaching qigong to individuals with limited mobility

- Currently teaches weekly qigong classes (60 – 90 minutes in length) open to any skill level
- Teaches a qigong form that includes physical movement (vs. meditation only)
- Classes allow for modifications and seated options for people with disabilities
- Instructor has safety protocols in place to ensure students can safely do movements
- Instructor is willing to keep track of attendance of study participants
- Qigong studio is ADA accessible
- Willingness to allow study participants to attend classes for free
- Show proof of individual and studio liability insurance with NUNM added to the policy
- Must complete HIPAA and sign a Disclosure of Significant Financial Interest (DSFI) compliance form.

C.4.2. EXCLUSION CRITERIA

- Qigong classes involving any kind of external martial or fighting component

Lita Buttolph has been a certified qigong instructor since 2005, and has personal and professional connections to other qigong instructors in Portland. Based on the above criteria, the following pre-vetted qigong instructors have been identified, and all have expressed a preliminary commitment to participate in the study. A detailed description and biography of each instructor is provided in the document "Qigong Forms Descriptions."

Tamara Staudt, ND,LAc- Jin Jing Gong Qigong
Classes taught at NUNM, Energy Medicine Room 305, Academic Building
Class format: Qigong classes all levels (ongoing)
Current class times: Tuesdays 5:30-6:45 pm

Eva Hosseinion, MD, LAc – Jin Jing Gong Qigong
Classes taught at NUNM, Energy Medicine Room 305, Academic Building
Class format: Qigong classes all levels (ongoing)
Current class times: Thursdays 7:00-8:00 pm

Francine Selke-Minogue - Wild Goose Qigong
Classes taught at Awakenings Wellness Center, 1016 SE 12th Ave., Portland, OR 97214
Class format: 16-week instructional classes beginning in late September and February
Current class times: Wednesdays 9 to 10:30 am

Tatiana Kulbakina-Tannenbaum, LMT - Wild Goose Qigong
Classes taught at People's Food Co-op Community Room, 3029 SE 21st. Ave., Portland, OR 97202
Class format: 16-week instructional classes beginning in late September and February
Current class times: Wednesdays 9 to 10:30 am

Keivan Jinnah, ND, LAc – Xin Yi Qigong
Classes taught at Sun Gate Studio, 2215 NE Alberta St., Portland, OR 97211
Class format: Qigong classes for all levels (ongoing)
Current class times: Mondays 9:45 – 11:00 am

All qigong instructors will be asked to sign a Memorandum of Understanding indicating that they comply with the criteria listed above and agree to participate in this study.

Prior to the beginning of the study, all instructors will participate in an orientation about teaching people with MS. This orientation will include a discussion about their involvement in the study; understanding and recognizing common symptoms experienced by MS patients; ways to support participants; how to recognize a participant having difficulty or overextending; and how to handle adverse events.

C.5. OUTCOME MEASURES FOR MS

C.5.1. Feasibility Outcome Measures

Feasibility outcome measures include (1) the ability to recruit and enroll participants with MS; (2) adherence to the intervention protocol as measured by class attendance and home practice; and (3) ability of participants to take part in qigong exercises. The following table outlines the criteria that we will use to assess each of these feasibility outcome measures:

Table 3. Feasibility outcome measure and assessment criteria

Feasibility Outcome Measure	Criteria Used to Assess Success
Ability to Recruit/Enroll Participants	20 enrollees within an 8-month period (or 2.5 enrollees per month)
Adherence to the Qigong Intervention	Attendance at a minimum of 7 out of 10 classes, and at least 2 days per week of home practice.[1] Attendance will be tracked by the instructor with a sign-in sheet, as well as by the participant with a wallet-size punch card. Participants will track their home practice with a practice log that we will provide.
Ability to Participate	Participants will subjectively rate their ability to participate in the exit survey. The student investigator will check-in with participants via phone during weeks 1, 2, and 7 of the 10-week intervention and ask about ability to participate. We define "ability to participate" as how easily participants feel they can follow along in class (i.e., fully able to participate, partially able to participate, only a little or not at all). Because qigong is a mind-body movement art, if participants are not physically able carry out a movement, they will be encouraged to visualize the movement. This is a common practice in qigong. Psychoneuroimmunology studies have shown physical benefits from visualization.[30] Thus, we consider visualization to be a valid form of participation. We will ask participants to estimate the proportion of movements that are visualized (0%, 25%, 50%, 75%, 100%) in the exit survey, and in their home practice log.

C.5.2. Intervention-Based Outcome Measures

The following measures were selected based on personal recommendations by neurologists at the OHSU MS Center, the recommendations of the International Consensus Meeting for a core set of outcome measures for use in exercise studies in MS (ICM),[31] and previous analyses of the

[1] We based this value on a meta-analysis of attrition and adherence rates for exercise interventions in which the authors found attrition ranging from 25-50% and an average adherence rate of 66%.[40]

PROMIS surveys for MS.[32] All measures are validated surveys or objective tests commonly used in MS research and include a combination of patient-reported surveys and timed physical tests. A computerized version of the MS-specific surveys will be used by participants to be consistent with the PROMIS online survey, and to reduce the time and potential for errors in transferring data from a paper survey to a digital database. Participants will complete the surveys on an iPad available at Helfgott Research Institute. The student investigator administering the survey will assist participants who need help completing the survey. We estimate the surveys to take 20 to 30 minutes to complete, and 15 to 20 minutes for the physical tests. .

C.5.2.a. Patient Self-Reported Surveys

Patient Reported Outcomes Measurement Information System (PROMIS)

Health related quality of life measures are commonly used to assess an individual's current health status, often in relation to a specific disease or treatment, and include patient self-reporting measures of physical, emotional and social well-being. For this study, we selected the Patient Reported Outcomes Measurement Information System (PROMIS), a series of free, online, patient reported outcome surveys funded by the National Institute for Health. This system has the ability to perform computerized adaptive tests, which have been shown to reduce survey time while maintaining outcomes consistent with conventional surveys. Senders et al. have validated its use for MS patients.[32] These authors also found that in addition to providing outcomes that correlated highly with legacy surveys, the computerized adaptive tests required less time to complete (i.e., 4 minutes versus 15 minutes); reduced missing data; and provided automatic scoring that referenced the general population.[32] For this study, we selected the following PROMIS instruments: global health, physical function, fatigue, anxiety and depression. Based on the findings of Senders et al., completion of all five surveys took an average of 4 minutes to complete.[32]

Multiple Sclerosis Impact Scale (MSIS-29)

The Multiple Sclerosis Impact Scale (MSIS-29) is a validated core outcome measure for quality of life in studies of exercise and MS.[31] The MSIS-29 was developed in 2000 as a patient-administered survey for MS, and includes 20 questions on physical impacts and 9 questions on psychological impacts of MS.[33] Estimated time to complete: 10 minutes.

MS Walking Scale (MSWS-12)

The MS Walking Scale is a 12-question survey of patient self-reported measure of impact of MS on walking ability.[34] The test has been rated as excellent on test-retest reliability, internal

consistency, and criterion validity.[31] We included this measure to complement the physical tests on balance and gait. Estimated time to complete: 5 minutes.

Modified Fatigue Impact Scale (MFIS 16)

The Modified Fatigue Impact Scale[35] has been recommended by the ICM as a measure of energy and drive. It is recommended over the Fatigue Severity Scale when conducting a multi-dimensional assessment of fatigue.[31] The survey consists of 21 questions that assess physical, cognitive and psychosocial aspects of fatigue. Estimated time to complete: 5 to 10 minutes.

C.5.2.b. Time-Based Physical Tests

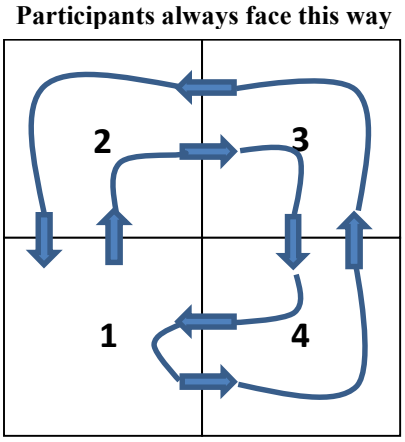
In addition to self-reported surveys, three time-based physical tests will be administered by the student investigator, with possible assistance provided by the principal investigator. Cinda Hugos, MS, PT, researcher and physical therapist at the MS Center at OHSU has agreed to help train the student investigator in administering these tests. Dr. Senders, who is familiar with some of these tests, will also provide training to the student investigator. If, based on the phone interview or arrival of the participant to the study visit, we anticipate the need for a second spotter, we will ensure that a spotter is available prior to the start of the test. Since we are recruiting individuals who state that they are able to walk 50 feet, unassisted, we anticipate less of a need for a second spotter than if this study included individuals with a higher degree of disability.

Four Square Step Test (FSST)

The Four Square Step Test is a test of a person's ability to step over objects in four directions. It is a common measure of multidirectional mobility for people with MS. Originally developed by Dite and Temple in 2002, the FSST has been shown to be reliable, valid, easy to score and administer.[36] The test consists of lining up 4 canes in a cross on the floor, with the central tips all converging, and creating four squares about 1 square yard in size (Figure 1). To reduce the risk of tripping on a cane, we will substitute the canes with colored masking tape to delineate the squares. The participant starts by standing in the lower left square (Square 1) and facing Square 2. The test starts with the participant stepping forward to square 2, stepping right to square 3, stepping back to square 4, stepping left to square 1, and then moving back in the opposite order (4 to 3 to 2 to 1) while being timed. The participant will be allowed to practice this sequence once before being timed. He/she will then be asked to complete the sequence as fast as possible with both feet touching each square without touching the borders. The test will be repeated

twice, with the best time taken as the score. The student investigator will administer the test and spot as needed, along with an extra spotter if the situation requires this. People unable to face forward during the sequence may turn to face the next box prior to stepping. The test may be repeated if the participant touches the tape, loses balance, or is unable to complete the sequence. Data collected will include number of seconds to complete the sequence and any observations. Estimated time to complete: 2 to 5 minutes.

Figure 1. Diagram of the Four Square Step Test



Timed 25-Foot Walk (T25-FW)

The Timed 25-Foot Walk is a reliable measure of walking ability and is regularly used as an outcome measure in studies of people with MS in relation to mobility.[37] The test is administered and rated by a trained examiner, and consists of having the subject walk a 25-foot long course as quickly and safely as possible while being timed. Once the subject reaches the end point, he/she is asked to turn around and walk back through the course, also while being timed. Subjects are allowed to use devices such as crutches, canes and walkers if needed. The test generally takes one to five minutes to complete. The score given for the test is an average of the time needed to complete each of the two trials. The T25-FW has been shown to have a high inter-rater and test-retest reliability, as well as good concurrent validity.[38] Estimated time to complete: 2-5 minutes.

Timed-Up and Go (TUG)

The Timed-Up and Go is a test of muscle function and mobility.[39] This test has been recommended by the ICM.[31] The test begins with the participant sitting in an armchair with his/her back resting on the back of the chair and arms resting on the arms of the chair. The

participant is then asked to stand up and walk 3 m at a comfortable and safe speed, turn around, walk back and return to a seated position. The time that it takes to complete this exercise is then recorded. Estimated time to complete: 2-5 minutes.

D.6. RANDOMIZATION AND BLINDING

Participants will be randomly assigned to the intervention or control group after baseline data are collected. Randomization will include blocking to ensure that both groups have an equal number of participants. Four people will be included in each block: two to the qigong intervention group and two to the control group. The creation of the allocation sequence and assignment of groups will be conducted by Helfgott statistician Dr. Doug Hanes. As this is a small pilot study, the student researcher will not be blinded when administering the surveys and physical tests. Participants will not be blinded since the control group will not participate in qigong classes.

D.7. DATA MANAGEMENT

Data collected for this study will include basic demographic information (e.g., name, age, gender, race, marital status, employment status, number/age of children), as well as current medication use. Data will also be collected from validated surveys and physical tests. All survey data (including the exit surveys and instructor surveys) will be administered through the Research Electronic Data Capture (REDCap) data management system. Data from physical tests will manually be entered into REDCap. Class attendance log information will be manually entered into REDCap.

D.7. STATISTICAL ANALYSES

Data will be analyzed using descriptive statistics for the feasibility outcomes, including mean number of enrollees per month, mean number of classes attended, mean number of hours of home practice per week, mean percent participation, and mean percent visualized movements. For effectiveness outcomes, the primary analysis will involve comparing intervention versus control group outcome measures using either an independent t-test or Mann-Whitney U (non-parametric) test. Additional analyses will include comparing pre- and post-outcome measures for the intervention group, as well as comparing pre- and post-outcome measures among the intervention plus wait-list controlled intervention group. Analyses of pre/post measures will be done using a paired t-test or Wilcoxon signed rank (non-parametric) test (see Table 2). In addition to testing for significant difference, we will also estimate effect sizes using Cohen's d statistics, calculated for

either within-group changes with treatment or differences between treatment and control groups. Depending on the range of disability in the study, analyses may be stratified by level of disability, based on disability questions included in the demographic survey. We will also explore the correlation between number of classes attended plus hours of home practice and outcome measures.

Table 4. Statistical analyses for Qigong intervention outcomes

Study Time Period	Group 1*	Group 2*	Statistical Test Used
Week 2-11	Tx1	Cx	Independent t-test or Mann-Whitney U test
Week 2-11	Tx1 (pre-intervention)	Tx1 (post-intervention)	Paired t-test or Wilcoxon signed rank
Week 2-11 + 13-22	Tx1+Tx2 (pre-intervention)	Tx1+Tx2 (post-intervention)	Paired t-test or Wilcoxon signed rank

*Tx1=Qigong intervention group; Cx = Wait-listed control group (no qigong); Tx2 = Cx before and after completed qigong intervention during weeks 15-26 of the study

D.8. POWER CALCULATION AND SAMPLE SIZE

We calculated power for the exploratory analysis of PROMIS Quality of Life (QOL) scores. Yost et al. estimated minimally important differences ranging from 3 to 6 points in selected PROMIS surveys for cancer patients.[41] Using 5 points as an approximate average of these differences and the standard deviations for the PROMIS QOL mental and physical health summary scores from Senders et al.[32] (4.00 and 3.06, respectively), we calculated that a total sample size of 16 (10 per group, minus 20% attrition) would provide 71% power to detect a mean increase of 5 in PROMIS QOL mental health and 90% power to detect a mean increase of 5 in PROMIS QOL physical health. (Power calculated using the University of British Columbia, Department of Statistics calculator, http://www.stat.ubc.ca/~rollin/stats/ssize/.)

E. HUMAN SUBJECTS

E.1. POTENTIAL RISKS AND HOW THEY WILL BE ADDRESSED

This study involves the use of questionnaires and surveys, physical tests, and an exercise intervention. The following table lists the potential risks associated with this study and how each risk will be minimized or addressed:

Table 5. Potential risks and measures to minimize/address risks.

Potential Risk	How risk will be minimized/addressed
Breach of confidentiality	We will make every effort to protect against the loss of confidentiality. All collection of participant personal information will comply with HIPAA regulations. Confidentiality will be assured by (1) assigning each participant a unique identification number used in place of names for all study forms and data collected; (2) keeping all forms and paper records containing participant information in a secure, locked file cabinet when not in use, which will be accessible only to the PI and student researcher; (3) using secure, password protected databases REDCap and PROMIS and storing any other electronic data on the Helfgott shared drive in password protected folders; (4) having all study personnel complete HIPAA training; (5) ensuring that participants are not identified by name in any reports or publications, nor are data presented in such a way that the identity of individual participants can be inferred.
Questions posed in surveys and questionnaires may seem personal or embarrassing to participants.	We will ensure that participants are made aware, in writing and verbally, that they do not need to answer any questions they do not feel comfortable answering. This information will be conveyed during the review of the Consent Form, as well as when the survey is administered
Participants may be injured during physical tests.	All study visits and testing will be conducted by Lita Buttolph, who will be trained to administer these tests. Cinda Hugos, a PT and researcher specializing in MS at OHSU has agreed to help train Lita Buttolph on how to administer the physical tests. Dr. Senders is also familiar with these tests and can help with training. Lita will ensure that participants are well aware of what is required for the test. She will also allow participants to practice a given test prior to timing. If a participant requires additional spotting assistance during the physical test, a testing assistant (either the PI or a trained student assistant) will be

	present to prevent any falls or injury. A licensed physician will be on site during all study visits. Lita will ensure prior to each study visit that a spotter will be available if needed.
Participants may be harmed or injured while partaking in the qigong classes.	Classroom safety will be carefully monitored by the instructor. We will select only instructors who are experienced with working with handicapped and health compromised students. The number of participants taking the 10-week qigong class will also be limited to no more than 3 per instructor, and may be less depending on the overall size of the class and the discretion of the instructor. Participants will be encouraged to self-monitor their own limits and abilities. All qigong forms selected for this study will have modified and seated options to accommodate individuals who are unable to stand for all or part of the class. Participants will have the option of sitting or standing during each class. Qigong instructors will receive an orientation prior to the start of the study about working with MS patients, including understanding and recognizing common symptoms experienced by MS patients; ways to support participants; how to recognize a participant having difficulty or overextending; and how to handle adverse events. The qigong instructors will encourage all participants to move and work within their own range of motion and ability. Participants and instructors will be asked to report any adverse events, and will be given the emails and phone numbers of the PI, student researcher, and Clinical Investigator. All adverse events will be reported to the IRB. Participants and instructors will be advised to call 911 or seek immediate medical assistance in the event of a medical emergency.

E.2. SAFETY PROTOCOL

Screening: The first level of safety is built into the screening procedures via inclusion and exclusion criteria.

Participant Check-ins: The student investigator will make phone calls to qigong group participants during Weeks 1, 2, and 7 of the study to check-in with participants and ensure that they feel safe

and comfortable in their classes. The student investigator will also encourage participants to call or email her if any discomfort, injury or concerns arise in a class.

Participant Spontaneous AE Reporting

Participants will be advised to contact Lita Buttolph and Dr. Senders for spontaneous reporting of any adverse events. Any adverse event that requires medical management or decision-making will be referred to Dr. Kalnins. In the event of a medical emergency, participants and instructors will be advised to call 911 or visit the closest emergency room.

Instructor Check-in: All qigong instructors will be instructed to contact the student investigator, study PI, or CI immediately if there are any health and/or safety concerns regarding the participants. We will also request that instructors check-in with each participant at each class to ensure they are not experiencing any problems.

Removal from the Study: In the event that a participant experiences pain, discomfort, injury or illness they will be seen by the clinical investigator who will decide on a case-by-case basis whether or not the participant should continue with or be excused from the study.

Privacy: Privacy in the context of this study includes confidentiality of data and personal information in handling and reporting of data as described above.

E.3. DEFINING AND REPORTING ADVERSE EVENTS

Adverse events will be reported according to the NUNM IRB Adverse Events Reporting Procedure. Adverse events are defined as follows (http://www.nunm.edu/helfgott-research/institutional-review-board-research-integrity/irb-adverse-events.php):

Adverse Event (AE): Any untoward medical occurrence in a study participant that may or may not have been caused by the study intervention. An AE may be an unfavorable and unintended sign (e.g., abnormal lab finding), symptom (e.g., back pain), or disease that happens during the study, whether or not related to the study intervention. There are 2 types of adverse events:

> **Anticipated**: Those already included in the protocol and consent form as a potential risk or part of the disease being studied.
>
> **Unanticipated:** Any serious event (including on-site and off-site adverse events, injuries, side effects, deaths or other problems) which, in the opinion of the local investigator, was

unanticipated, serious, and was at least possibly related to the research procedures, including:

- Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur;
- Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject;
- Any publication in the literature, safety monitoring report (including Data and Safety Monitoring Reports), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Any breach in confidentiality that may involve risk to the subject or others;
- Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the research staff; or
- Any other serious and possibly related event which in the opinion of the investigator constitutes an unanticipated risk.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. Other important medical events requiring medical or surgical intervention to prevent a serious outcome are also included. Specific definitions of SAEs include the following:

- Death: An event that results in the death of a subject
- Life Threatening: An event, which, in the opinion of the physician, would have resulted in immediate fatality if medical intervention had not been taken.
- Hospitalization: An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or an admission to an outpatient facility.
- Prolongation of Hospitalization: An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
- Persistent or Significant Disability: An event that results in a condition that substantially interferes with the activities of daily living of a subject. "Disability" is not intended to include experiences of relatively minor medical significance such as headache, vomiting or accidental trauma (e.g. sprained ankle).
- Congenital Anomaly: An anomaly detected at or after birth or any anomaly that results in fetal loss.

- Important Medical Event: An important medical event may not be immediately life-threatening or result in death or hospitalization but requires intervention(s) to prevent serious outcome based on medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above.

Severity: Adverse events, *but not SAEs*, are categorized into four levels of severity: mild, moderate, severe, or very severe. These categories are defined as follows:

- Mild: Transient and easily tolerated.
- Moderate: Results in a modification or interruption of the subject's usual activities or care and may require discontinuation of the study intervention
- Severe: Results in considerable interference with the subject's usual activities or care and may require discontinuation of study intervention.
- Very Severe: Results in the need for urgent medical care and likely requires discontinuation of the study intervention.

Attribution: The relationship between adverse events and the study intervention should be evaluated and graded as none, remote, possible, probable, or highly probable. Clinical investigators are responsible for determining the relationship between study intervention and adverse events.

The timeline for reporting AEs and SAEs is as follows:

Anticipated Adverse Events: These will be reported in summary form annually to the IRB during continuing review, regardless of whether classified as severe or related to the study intervention.

Unanticipated Adverse Events: Unanticipated problems will be reported to the IRB within 10 working days of the investigators being notified of the event.

Serious Adverse Events: Serious adverse events will be reported the IRB within 24 hours of the investigators being notified.

E.3. RECRUITMENT AND INFORMED CONSENT

The NUNM Institutional Review Board will approve all recruitment procedures and the study protocol. The student investigator will subsequently gain consent from the participant during the first visit before any data are collected. She will meet in a private room with the potential

participant and review all aspects of the consent form in detail. She will explain that participation is voluntary, may be terminated at any time, and will not affect their ability to participate in future research studies. The student investigator will determine the participant's ability to provide informed consent by asking the following questions:

- Do you understand what is being asked of you in this study?
- Do you have any questions for me about what is going to happen?
- Can you tell me how long you will be asked to be in this study?
- Could you tell me how long you will be asked to participate in a qigong class?

Once the student investigator feels certain that potential participants clearly understand their roles, rights and responsibilities, she will ask them to sign an approved written consent form. The potential participant will sign the consent form if they agree to the terms stated. The student investigator will retain the signed consent form, and a copy of the signed consent will be provided to the participant. The original copy will be filed in a locked filing cabinet in the PI's office.

E.4. POTENTIAL BENEFITS TO PARTICIPANTS

Participants may or may not receive any benefit from partaking in this study.

E.5. INCENTIVES

Neither Qigong Instructors nor study participants will receive incentives for participating in this study.

F. IMPORTANCE OF KNOWLEDGE GAINED

By understanding if and how qigong can affect symptoms of MS, this study can help broaden the range of possible therapies available to people with MS. Results from this trial will provide preliminary data, direction and feasibility to seek future funding for a fully powered randomized controlled trial of qigong and MS.

G. PERSONNEL

G.1. PRINCIPAL INVESTIGATOR

Angela Senders, N.D., M.C.R., is an Assistant Dean in the School of Research & Graduate Studies and chair of the Integrative Mental Health Program at the National University of Natural Medicine (NUNM). She received her doctorate in naturopathic medicine from NUNM in 2005 and maintained a private practice for six years with a focus on mind-body medicine. In 2011 she was awarded a postdoctoral fellowship with the Oregon Center for Complementary and Alternative Medicine in Neurological Diseases at Oregon Health & Science University (OHSU) to study mind-body medicine in a larger health care context. She completed a master of clinical research in 2014 and currently funded by the NIH to investigate the impact of psychological stress and mindfulness in multiple sclerosis.

G.2. STUDENT INVESTIGATOR

Lita Buttolph, Ph.D., has been involved in ecological and social science research for the past 25 years. She received her B.A. in ecology and M.S. in Wildland Resource Science at the University of California, Berkeley. For her Master's degree she was involved in several research studies ranging from ecological studies of plant-animal dynamics to social science studies related to land use policy, livestock grazing and fire management. After completing her Master's degree, she worked as a research assistant conducting research on poverty and community well-being in rural communities in the Sierra Nevada Mountains in California. In 1993, she began her doctorate in Rangeland Science, specializing in International Rangeland Management at Utah State University. For her dissertation research, Dr. Buttolph studied traditional land use management practices and the effects of an international development project on indigenous Aymara pastoralists in the Bolivian Andes. After completing her doctorate, Dr. Buttolph worked for 15 years conducting research and outreach in natural resources management and policy in the Pacific Northwest. She participated in long-term evaluations of the socioeconomic impacts of the federal Northwest Forest Plan and Economic Adjustment Initiative. Subsequent work included working with family forest land owners to find alternative income sources from their land through the harvesting and sale of non-timber forest products, including wild food, and medicinal herbs. Dr. Buttolph has been a qigong practitioner since 1999, and has been a qigong instructor since 2004. She is currently pursuing a doctorate in Oriental Medicine and a master's in Integrative Medicine Research at the National University of Natural Medicine in Portland, Oregon.

G.3. CLINICAL INVESTIGATOR

Paul Kalnins, N.D., M.S.O.M., received his N.D. and M.S.O.M. degrees from the National University of Natural Medicine (NUNM) in 1998. He currently serves as assistant professor and clinical supervisor at NUNM, where he lectures on a variety of topics ranging from physiology, embryology, pathology and pharmacology. He is a member of the Helfgott Research Institute and has pursued the integration of traditional naturopathic and Chinese medical practices with evidence-based biomedicine. In particular, he has explored the synthesis of traditional concepts of temperament and terrain, with modern research in genetics-epigenetics, neuroendocrine-immunology, hormesis, and chronobiology.

H. CITED REFERENCES

1. National MS Society. What is Multiple Sclerosis? : National MS Society. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/what-is-ms/index.aspx. Accessed February 3, 2014.

2. Amano S, Nocera JR, Vallabhajosula S, et al. The effect of Tai Chi exercise on gait initiation and gait performance in persons with Parkinson's disease. *Parkinsonism Relat Disord*. 2013;19(11):955–60. doi:10.1016/j.parkreldis.2013.06.007.

3. Li F, Harmer P, Fitzgerald K, et al. Tai chi and postural stability in patients with Parkinson's disease. *N Engl J Med*. 2012;366(6):511–9. doi:10.1056/NEJMoa1107911.

4. Ni X, Liu S, Lu F, Shi X, Guo X. Efficacy and safety of tai chi for Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9(6):e99377. doi:10.1371/journal.pone.0099377.

5. Schmitz-Hübsch T, Pyfer D, Kielwein K, Fimmers R, Klockgether T, Wüllner U. Qigong exercise for the symptoms of Parkinson's disease: a randomized, controlled pilot study. *Mov Disord*. 2006;21(4):543–8. doi:10.1002/mds.20705.

6. Chan JSM, Ho RTH, Wang C-W, Yuen LP, Sham JST, Chan CLW. Effects of qigong exercise on fatigue, anxiety, and depressive symptoms of patients with chronic fatigue syndrome-like illness: a randomized controlled trial. *Evid Based Complement Alternat Med*. 2013;2013:485341. doi:10.1155/2013/485341.

7. Ho RTH, Chan JSM, Wang C-W, et al. A randomized controlled trial of qigong exercise on fatigue symptoms, functioning, and telomerase activity in persons with chronic fatigue or chronic fatigue syndrome. *Ann Behav Med*. 2012;44(2):160–70. doi:10.1007/s12160-012-9381-6.

8. Oh B, Butow P, Mullan B, et al. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. *Ann Oncol*. 2010;21(3):608–14. doi:10.1093/annonc/mdp479.

9. Mills N, Allen J. Mindfulness of Movement as a Coping Strategy in A Pilot Study. *Gen Hosp Psychiatry*. 2000;22(00):425–431.

10. National Institute of Health. Multiple Sclerosis: Hope Through Research. *NIH - Natl Inst Neurol Disord Stroke*. 2014. Available at: http://www.ninds.nih.gov/disorders/multiple_sclerosis/detail_multiple_sclerosis.htm#264603215. Accessed December 18, 2014.

11. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. *UpToDate*. 2014. Available at: http://www.uptodate.com.ezproxy.ncnm.edu/contents/treatment-of-relapsing-remitting-multiple-sclerosis-in-adults?source=search_result&search=MS+medication+side+effects&selectedTitle=1~150. Accessed December 18, 2014.

12. Olek MJ. Treatment of progressive multiple sclerosis in adults. *UpToDate*. 2014. Available at: http://www.uptodate.com.ezproxy.ncnm.edu/contents/treatment-of-progressive-multiple-sclerosis-in-adults?source=see_link. Accessed December 18, 2014.

13. National MS Society. Symptoms : National MS Society. Available at: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/symptoms/index.aspx. Accessed February 3, 2014.

14. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult Scler Int*. 2014;2014:798285. doi:10.1155/2014/798285.

15. Beckerman H, Blikman LJ, Heine M, et al. The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme. *Trials*. 2013;14:250. doi:10.1186/1745-6215-14-250.

16. Carter AM, Daley AJ, Kesterton SW, Woodroofe NM, Saxton JM, Sharrack B. Pragmatic exercise intervention in people with mild to moderate multiple sclerosis: a randomised controlled feasibility study. *Contemp Clin Trials*. 2013;35(2):40–7. doi:10.1016/j.cct.2013.04.003.

17. Carter A, Daley A, Humphreys L, et al. Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised controlled trial. *Mult Scler*. 2014;20(8):1112–1122. doi:10.1177/1352458513519354.

18. Ensari I, Motl RW, Pilutti LA. Exercise training improves depressive symptoms in people with multiple sclerosis: results of a meta-analysis. *J Psychosom Res*. 2014;76(6):465–71. doi:10.1016/j.jpsychores.2014.03.014.

19. Latimer-Cheung AE, Pilutti LA, Hicks AL, et al. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: a systematic review to inform guideline development. *Arch Phys Med Rehabil*. 2013;94(9):1800–1828.e3. doi:10.1016/j.apmr.2013.04.020.

20. Marck CH, Hadgkiss EJ, Weiland TJ, van der Meer DM, Pereira NG, Jelinek GA. Physical activity and associated levels of disability and quality of life in people with multiple sclerosis: a large international survey. *BMC Neurol*. 2014;14(1):143. doi:10.1186/1471-2377-14-143.

21. Mayo NE, Bayley M, Duquette P, Lapierre Y, Anderson R, Bartlett S. The role of exercise in modifying outcomes for people with multiple sclerosis: a randomized trial. *BMC Neurol*. 2013;13:69. doi:10.1186/1471-2377-13-69.

22. Pilutti L a, Dlugonski D, Sandroff BM, Klaren R, Motl RW. Randomized controlled trial of a behavioral intervention targeting symptoms and physical activity in multiple sclerosis. *Mult Scler*. 2014;20(5):594–601. doi:10.1177/1352458513503391.

23. Wayne PM, Buring JE, Davis RB, et al. Tai Chi for osteopenic women: design and rationale of a pragmatic randomized controlled trial. *BMC Musculoskelet Disord*. 2010;11:40. doi:10.1186/1471-2474-11-40.

24. Guo L-Y, Yang C-P, You Y-L, et al. Underlying mechanisms of Tai-Chi-Chuan training for improving balance ability in the elders. *Chin J Integr Med*. 2014;20(6):409–15. doi:10.1007/s11655-013-1533-4.

25. González López-Arza MV, Varela-Donoso E, Montanero-Fernández J, Rodríguez-Mansilla J, González-Sánchez B, González López-Arza L. Qigong improves balance in young women: a pilot study. *J Integr Med*. 2013;11(4):241–5. doi:10.3736/jintegrmed2013038.

26. Wu C-Y, Han H-M, Huang M-C, Chen Y-M, Yu W-P, Weng L-C. Effect of qigong training on fatigue in haemodialysis patients: A non-randomized controlled trial. *Complement Ther Med*. 2014;22(2):244–50. doi:10.1016/j.ctim.2014.01.004.

27. Sawynok J, Lynch M, Marcon D. Extension trial of qigong for fibromyalgia: a quantitative and qualitative study. *Evid Based Complement Alternat Med*. 2013;2013:726062. doi:10.1155/2013/726062.

28. Haak T, Scott B. The effect of Qigong on fibromyalgia (FMS): a controlled randomized study. *Disabil Rehabil*. 2008;30(8):625–33. doi:10.1080/09638280701400540.

29. Mills N, Allen J, Carey-Morgan S. Does Tai Chi/Qi Gong help patients with Multiple Sclerosis? *J Bodyw Mov Ther*. 2000;4(1):39–48. doi:10.1054/jbmt.1999.0139.

30. Warner L, McNeill ME. Mental imagery and its potential for physical therapy. *Phys Ther*. 1988;68(4):516–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3281175. Accessed December 18, 2014.

31. Paul L, Coote S, Crosbie J, et al. Core outcome measures for exercise studies in people with multiple sclerosis: recommendations from a multidisciplinary consensus meeting. *Mult Scler*. 2014. doi:10.1177/1352458514526944.

32. Senders A, Hanes D, Bourdette D, Whitham R, Shinto L. Reducing survey burden: feasibility and validity of PROMIS measures in multiple sclerosis. *Mult Scler*. 2014;20(8):1102–1111. doi:10.1177/1352458513517279.

33. Hobart J, Lamping D, Fitzpatrick R, Riazi A, Thompson A. The Multiple Sclerosis Impact Scale (MSIS-29): A new patient-based outcome measure. *Brain*. 2001;124(5):962–973. doi:10.1093/brain/124.5.962.

34. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology*. 2003;60(1):31–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12525714. Accessed November 13, 2014.

35. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis*. 1994;18 Suppl 1:S79–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8148458. Accessed November 16, 2014.

36. Dite W, Temple VA. A clinical test of stepping and change of direction to identify multiple falling older adults. *Arch Phys Med Rehabil*. 2002;83(11):1566–71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12422327. Accessed November 13, 2014.

37. Mañago MM, Hebert JR. Concurrent validity of the patient-specific functional scale and the timed 25 foot walk test in people with Multiple Sclerosis. In: *Symposium of Gait and Balance in Multiple Sclerosis*.; 2013.

38. National MS Society. T25-FW : National MS Society. Available at: http://www.nationalmssociety.org/ms-clinical-care-network/researchers/clinical-study-measures/t25-fw/index.aspx. Accessed February 4, 2014.

39. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142–8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1991946. Accessed July 31, 2014.

40. Linke SE, Gallo LC, Norman GJ. Attrition and adherence rates of sustained vs. intermittent exercise interventions. *Ann Behav Med*. 2011;42(2):197–209. doi:10.1007/s12160-011-9279-8.

41. Yost KJ, Eton DT, Garcia SF, Cella D. Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *J Clin Epidemiol*. 2011;64(5):507–16. doi:10.1016/j.jclinepi.2010.11.018.