**Cubii for Exercise in People With MS**

**NCT0582643**

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**Cubii-MS**
**Study Protocol**
**Principal Investigator: Kevin Alschuler, Ph.D., University of Washington**

## 1. Background and Specific Aims

Nearly one million people in the United States (U.S.) live with multiple sclerosis (MS),[1] a typically progressive disease that can cause widespread impairment across physical and psychological domains (e.g., mobility impairments, fatigue, pain, anxiety and/or depression, cognitive dysfunction). Unfortunately, there is currently no cure for MS, and the disease often has a significant negative impact on functioning and quality of life.[2] Some pharmacologic treatments aim to reduce or stop the rate of disease progression, while other pharmacologic and nonpharmacologic interventions focus on improving symptom management and functioning

Data indicates people with MS are less active than their peers in the general population. Exercise interventions are important non-pharmacologic approaches to maximize function and quality of life for people living with MS. Based on current evidence and expert opinion, the National Multiple Sclerosis Society (NMSS) recommends that healthcare providers promote the benefits of exercise and lifestyle physical activity for every person with MS.

Individuals with at least moderate impairment (approximately 50% of the MS population) often require adaptive exercise due to mobility and balance impairments. Typically, these individuals experience limitations in walking distance and present with neurologic impairments that impact their gait and/or coordination. This may necessitate precautions for falls, as well as the use of assistive devices or compensatory strategies. The Cubii product line is well-placed for this subset of the MS population as it allows for safe, seated exercise that can still meet the recommendations for aerobic and resistance training.

To address this need, this study will capitalize on a representative, heterogeneous sample of MS patients who are seeking to change their coping behaviors around MS, including by exercising more, and an existing exercise unit that can be utilized by people with a range of mobility.

The **specific aims** of this prospective observational study are to evaluate
**(1)** the feasibility, usability, and satisfaction with the Cubii elliptical and
**(2)** the preliminary efficacy of the Cubii elliptical for increasing activity (primary outcome), physical function, and quality of life, and decreasing physical and psychological symptom (e.g., pain, fatigue, depression) severity in people with MS.

## 2. Study Design & Methods

To achieve the study aims, we will conduct a prospective observational study that combines self-reported measures and the use of the Cubii exercise unit.

Participation in this study will involve (1) presenting to the UW Medicine Multiple Sclerosis Center ("MS Center") to complete "baseline" assessments (T1; see section X.X) and receive their Cubii exercise unit; (2) self-directed use of the Cubii exercise unit at home for 8 weeks; and (3) returning to the MS Center to complete a walking test and an assessment (T2).

Study coordinators will maintain a relationship with participants to ensure adherence to the study protocol. This may include contact participants (according to their preferred method) at the midpoint of the self-directed home exercise period to troubleshoot any issues that may have arisen.

Participants will be compensated $100 for full completion of the study ($40 for participating at T1 and $60 after completing the assessments at T2).

### 2.1. Study Sample and Recruitment

We will recruit and enroll N = 20 individuals with MS from the MS Center. We will use the existing participant registries (N > 1,500), electronic health record queries, institution-specific subject-recruitment websites, and provider referrals.

**Table 1.** Study Inclusion and Exclusion Criteria

| **Inclusion Criteria** |
|---|
| 1. 18 years of age or older |
| 2. Can fluently converse and read in English (to complete study questionnaires) |
| 3. Clinician-confirmed MS |
| 4. Walks with the aid of an assistive device (e.g., cane, walker, forearm crutches) |
| 5. Lives in the greater Seattle metropolitan area |
| 6. All genders |
| 7. Has an iPhone or Android phone able to download an app |
| **Exclusion Criteria** |
| 1. People unable to exercise for health reasons |

## 3. Enrollment and Data Collection Procedures

### 3.1. Screening

Research staff will reach out to interested participants and provide them with more information about the study and answer their questions. During the initial phone contact, staff will provide a brief overview of the study. If a participant is interested in going through the screening process, research staff will, with the participant's permission, ask them screening questions to determine eligibility and to obtain basic demographic information (e.g., age, sex, gender, geographic location).

For eligible participants, we will collect additional contact information (e.g., confirm name, email, phone number(s)). Research staff will also document the outcome of the screening and the reason for ineligibility or decline.

### 3.2. Study Procedures and Materials

**Pre-baseline visits tasks** Participants will first complete validated self-report questionnaires (demographics, MS disease-related variables (e.g., pain, fatigue, falls), activity, exercise, quality of life, and biopsychosocial symptom variables).

**In-person baseline visit**

At the baseline visit (T1), participants will come to the MS Center for a 60-minute visit during which they will take a six-minute walking test, and engage with staff for a brief orientation to the Cubii and its phone app.

**Eight-week at-home period**

Participants will use the Cubii at home for two months. Participants will use the unit as they choose and maintain a log regarding their device use.

**In-person post-treatment visit**

Participants will return to the UW MS Center at nine weeks and complete the same validated self-report questionnaires at baseline and provide additional data regarding the feasibility, usability, and satisfaction with the use of the Cubii.

**Table 2.** Study Activities

| Primary Outcomes | Domain | Study Activity | Baseline (week 1) | Weeks 2-8 | Week 9 |
|---|---|---|---|---|---|
| | | Demographics | X | | X |
| | | Medical/Surgical History/Disease variables | X | | |
| | | Anticipated experience/use/satisfaction | X | | |
| | | Patient Global Impression of Change (PGIC) | X | | X |
| Additional covariates | Satisfaction with social roles | PROMIS Satisfaction with Participation in Social Roles Short Form 8a | X | | X |
| | Self-efficacy | University of Washington Self-Efficacy Scale short form | X | | X |
| | Resilience | UW Resilience Scale 8-item short form v1.0 | X | | X |
| | Comorbidities | Comorbidity Questionnaire | X | | X |

| | | | | | |
|---|---|---|---|---|---|
| | Physical Activity Readiness scale | PAR-Q+ | X | | X |
| Preliminary efficacy | Physical activity | Godin Leisure Time Exercise Questionnaire | X | | X |
| | Physical function | PROMIS Short Form v2.0 - Physical Function 20a | X | | X |
| | Quality of life | MSQOL54- Quality of Life Subscale | X | | X |
| | Pain intensity | PROMIS Pain Intensity Short Form 3a | X | | X |
| | Pain interference | PROMIS Pain Interference Scale (Short Form 8b, V1.0) | X | | X |
| | Fatigue interference | PROMIS SF v1.0 - Fatigue-Multiple Sclerosis 8a | X | | X |
| | Depression | PROMIS Short Form v1.0 Depression 8a | X | | X |
| | Anxiety | PROMIS Short Form v1.0 - Anxiety 8a | X | | X |
| | Ambulatory function | CogDetect walking tests | X | | X |
| | Fatigue intensity | Brief Fatigue Inventory (BFI) | X | | X |
| | | Measure of falls | X | | X |
| | | Spaciticty | X | | X |

### 3.3. Data Collection Technology

We will collect survey data via a secure REDCap website. REDCap is an open-source, secure, HIPAA-compliant web-based platform designed to support data capture for research studies. Vanderbilt University designed it to protect patient privacy and confidentiality while assisting investigators in clinical research. It provides an interface for data entry and validation, auditing features for tracking data manipulation, the ability to import data from external sources, calculated data fields, branching logic, and the capability to export data to many statistical packages. System and application-level security include SSL encryption of internet traffic (https pages), hosting in a secure data center with nightly backup, fine-grained control over user rights, detailed audit trails, record locking, and de-identification features for data export.

### 3.4. Lab Visit Measures

We will assess several baseline measures to characterize the study samples.

#### 3.4.1. Self-Report Measures

The participants will complete online self-report surveys via REDCap. Study staff will register participants in REDCap and provide a participant-specific URL to access the surveys. The survey battery will take approximately 20 minutes and study staff will be available to assist as needed. See above table for measures and participant demographics and clinical characteristics: demographic questions (age, sex, gender, race, ethnicity, education, income, marital status,

employment status & healthcare coverage), clinical survey (e.g., time since diagnosis, MS subtype, brief medical and psychiatric history, and other clinical characteristics), and treatment survey (e.g., medications and therapies). .

**Ambulatory measures**
**Motor Function:** We will administer a 4-m backward walking test, evaluation of gait speed (4 meter walk test), and gait endurance (2-minute walk test).

> **Backward gait speed:** Backward walking is used to assess balance and fall risk. Participants walk backwards a short distance at their usual pace, completing one practice and two-timed trials. Scores are recorded as time in seconds required to walk 4 meters on each of two trials, with the better trial used for scoring. The test time is ~3 minutes.
>
> **Gait speed:** The 4-meter walking test measures locomotion. Participants walk a short distance at their usual pace, completing one practice and two-timed trials. Scores are recorded as time in seconds required to walk 4 meters on each of two trials, with the better trial used for scoring. The test time is ~3 minutes.
>
> **Gait endurance** (2-minute walk test): This test assesses the ability to sustain effort that requires conjoint work capacities from cardiopulmonary function, biomechanical, and neuromuscular function. The test time is ~4 minutes.

## 4. Data Management: Storage and Sharing

We will use REDCap to collect and store study data and participant identifiers. We will (1) assign each participant an ID number in REDCap to maintain confidentiality and (2) use this ID number to code/label study data. The link between the study data and a participant's identity will only exist in REDCap, to which only research staff members have access.

We will label any paper forms only with the ID number and keep them in a locked cabinet separate from any identifying information and will scan and upload them to REDCap as a source document.

We will track protocol deviations and adverse events in REDCap.

## 5. Data Analysis/Statistical Methods

### 5.1. Sample Size Determination

The study sample size (N = 20) is consistent with pilot studies that seek to examine feasibility, usability, and satisfaction of an intervention or device, and provides an opportunity to collect preliminary data on efficacy. Consistent with pilot studies in general, this sample size is underpowered to make definitive conclusions about the effect of the device on primary outcomes; in contrast, it is sufficient for serving as the basis for future applications for full-size trials that are sufficiently powered to test such outcomes.

### 5.2. Analysis of Study Aims

To describe the sample, we will report the number of participants approached (and recruitment

source), eligible, excluded, declined, enrolled, randomized, and who provided data at each assessment point (including reasons for exclusion and declination). Before conducting the primary analyses, we will examine distributions of all variables for outlying values and skewness; where indicated, we will recode or transform variables. For aim 1, we will calculate descriptive and frequency analyses. For aim 2, we will conduct analyses to assess for statistically significant within-person change on the target outcomes (activity (primary outcome), physical function, and quality of life, and decreasing physical and psychological symptom (e.g., pain, fatigue, depression) severity).

## 6. Human Subjects Protections

### 6.1. Potential risks

The risks associated with the proposed study are minor and infrequent.

Confidentiality is a concern in this study. We will make every effort to keep the research information in the strictest confidence, but we cannot guarantee that accidental disclosure will not happen. We remind participants that the responsibility of confidentiality rests with everyone: they should think carefully before discussing their role in this study with anyone since the effects of disclosure are unknown.

Participants may experience fatigue and/or boredom while completing the assessments, exercise sessions, and logs. Some participants may experience mild muscle soreness from the exercise and may also experience mild anxiety, frustration, and/or stress while answering questions about exercise and mood.

### 6.2. Adequacy of Protection Against Risk

#### 6.2.1 Informed Consent

The UW IRB approved the protocol for this study. Research staff members will ask interested people a set of formalized questions to determine eligibility based on the inclusion/exclusion criteria. They will obtain non-written consent to ask potential participants eligibility questions before initiating the screening process. Individuals who are interested in participating will be allowed to ask any questions about the study and their participation, and if they opt to enroll, they will provide written informed consent before completing any study assessments; a copy of their signed informed consent document will be provided to the participant.

#### 6.2.2. Protection against Risks

To minimize the potential for risks, we will brief participants in detail as to what they will experience throughout the study. We will inform all participants that they may terminate participation in the study at any time without penalty.

To reduce the risk to confidentiality, we will

1. assign each participant an ID number to maintain confidentiality
    a. use this ID number to code/label study data
    b. keep this link between the study data and a participant's identity in the form of the unique study code that will only exist in REDCap, to which only research staff members have access. REDCap is a secure, web-/cloud-based system approved for research use, with access limited to the study team.

2. use REDCap to collect and store study data and participant identifiers.
3. label any paper forms only with the ID number and keep them in a locked cabinet (in which only research staff will have keys) separate from any identifying information and will scan and upload them to REDCap as a source document.

Throughout the consent process and study, we will inform participants that they do not have to discuss any topics they do not wish to. In addition, we will inform participants during the consent process that they are free to stop any session or assessment at any time. Participants may refuse to answer any questions that make them feel uncomfortable.

We will inform all participants of their right to withdraw from the study at any point without adversely impacting their routine medical, psychiatric, or psychotherapeutic care.

If participants experience fatigue or frustration during lab-visit assessments, we will encourage them to take a break, and remind them that they do not have to answer any questions they do not wish to answer and that they may terminate participation in the study at any time without penalty.

We will instruct the participant to contact the study team if they experience any negative experiences from using the Cubii unit. Study team members will attempt to troubleshoot issues related to discomfort with using the unit, such as ensuring the foot straps are not too tight and good posture while seated. We will minimize this risk by telling the participants that it may take a few days to get used to using the Cubii.

Although the study poses no serious risks to participants, participants may notify research personnel about pre-existing mental health issues that have not been previously identified. Staff will implement a suicide risk assessment protocol (see document "Suicide Protocol"). Some participants may have difficulty moving the 29lbs unit from and into their vehicle. We will screen participants to ensure they can, or someone can assist them to, move the unit without risk.

## 7. Monitoring Plan and Information

All research personnel involved in any way in this project will have completed training in the protection of human research participants per guidelines issued by the U.S. Department of Health and Human Services, Office for Human Research Protection. The IRB and other necessary regulatory and oversight entities will review and approve this protocol before implementation.

The principal investigator will check with staff weekly to discuss study activities, progress, and troubleshoot any issues including recruitment efforts, data collection (including data management and clearing of queries), and discussion of any protocol deviations or adverse events. Additionally, ongoing training will occur as needed.

## 8. Importance of Knowledge to be Gained

The findings from this study can advance implementation of rehabilitation strategies to restore function, reverse symptoms, and enhance quality of life for people with MS.

## 9. Study Discontinuance and Closure

In the event a participant withdraws from the study or is lost to follow-up, staff will make all attempts to exit the participant in accordance with the protocol requirements and record the reason for discontinuation.

### 10.1. Adverse Event Reporting

For this study, staff will report only **related** adverse events. "Related" means events caused by the research itself, not the disease or population under study. Staff will report to the IRB using the standard IRB reporting schedule.

### 10.2. Unanticipated Problems and Protocol Deviation Reporting

Regulations require investigators to report unanticipated problems involving risks to participants or others, as well as any other event or information that may increase risks, may alter the risk-benefit assessment, may affect the participant's willingness to participate in the research, or may represent a departure from applicable human subject protections regulations or policies (i.e., a protocol deviation).

We will report all instances to the IRB with the following exceptions:

1. Participants who skip study assessments
2. Participants who decline the participant payment. It has been our experience that some research participants do not wish to receive payment for their participation in their study

## 11. Quality Control Procedures

Cubii staff will train the study staff on the unit as outlined in the Manual of Procedures (MOP). Managers will monitor staff throughout the course of the study through regular team meetings.