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# REFRESH protocol: a non-inferiority randomised clinical trial comparing internet and teleconference to in-person 'Managing Fatigue' interventions on the impact of fatigue among persons with multiple sclerosis

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## ABSTRACT

**Introduction** Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system. It is considered a major cause of non-traumatic disability in young adults. One of the most common and disabling symptoms of MS is fatigue. MS fatigue can impact all aspects of quality of life, including physical, mental and social function. Fortunately, fatigue self-management interventions, such as '*Managing Fatigue: A 6 week energy conservation course*', can decrease the impact of fatigue and improve health-related quality of life. The purpose of this study is to compare three modes of delivering the *Managing Fatigue* intervention—two remote delivery formats (teleconference and internet) and one in-person format—on perceptions of fatigue and its impact on physical, mental and social function.

**Methods and analysis** A non-inferiority randomised clinical trial is being conducted to compare the three delivery formats (1:1:1 allocation ratio) among 582 participants with MS living in the Midwestern and Northeastern United States. The hypothesis is that teleconference and internet versions of the intervention are non-inferior to the traditional mode of clinical service delivery (ie, one to one, in person) in terms of the primary outcome of self-reported fatigue impact (ie, Fatigue Impact Scale) and the secondary outcome of health-related quality of life (ie, Multiple Sclerosis Impact Scale). Outcomes are being measured at baseline, 2 months, 3 months and 6 months. The primary analysis tool will be linear mixed effects model. The prespecified inferiority margin for the primary outcome is 10 points. We will also examine whether baseline characteristics (eg, sociodemographic) moderate outcomes of the *Managing Fatigue* intervention and whether changes in self-efficacy and fatigue self-management behaviours mediate changes in outcomes.

**Ethics and dissemination** The protocol is approved centrally by the institutional review board at Case Western Reserve University. Eligible participants give consent before being enrolled and randomised into the study. The study results will be disseminated through relevant advocacy organisations, newsletters to participants, publication in peer-reviewed journals and presentations at scientific conferences.

**Trial registration number** NCT03550170; Pre-results.

## Strengths and limitations of this study

- This is the first randomised clinical trial to compare three formats of delivering the *Managing Fatigue* intervention.
- The study is designed to include underserved population segments, such as people with physical disabilities, mental health problems, or cognitive difficulties, as well as racially and ethnically diverse people from both rural and urban areas, but will exclude people if they cannot speak and read English.
- With a finding of non-inferiority, the more easily accessible teleconference and internet versions of the *Managing Fatigue* intervention can be recommended instead of the traditional mode of clinical service delivery.
- Results could be used as a rationale to deliver remote formats of the Managing Fatigue intervention to people who typically cannot access these interventions due to geographic, socioeconomic, transportation or disability-related barriers.
- The study design does not include a non-intervention control group, and expectations and preferences for a particular delivery format might influence the results.

## INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system.[1] An estimated 2.2 million people have MS worldwide.[2] It is a major cause of non-traumatic disability in young adults.[3] One of the most common and disabling symptoms of MS is fatigue.[4] MS fatigue can impact all aspects of daily activities and quality of life,

including physical, mental and social function.[5 6] MS fatigue is defined as a lack of physical and/or mental energy and is assocatied with overwhelming feelings of tiredness and exhaustion that interfere with usual and desired activities.[7–9] MS fatigue can create profound barriers to maintaining employment, participating in social activities and engaging in self-care activities.[5 10–12] MS fatigue is associated with worse treatment outcomes, exacerbations, increased comorbidities and decreased adherence to disease-modifying therapies.[13–16]

The pathophysiology of MS fatigue still remains unclear, but several studies indicate that MS fatigue is most likely the result of multiple factors. These factors can be classified as primary or secondary causes of MS fatigue.[17] Primary causes of MS fatigue pertain to pathology and maladaptive responses, such as brain lesions, axonal damage, cortical reorganisation, imbalances in dopamine and increased inflammation.[18 19] Secondary causes pertain to the presence of other concomitant circumstances or disorders, such as sleep difficulties, inactivity and mood disorders.[8 9 17] Although there is some overlap between MS fatigue, sleepiness and mood disorders, it is thought that MS fatigue is a distinct and separate entity.[4 20–22]

Randomised controlled trials of existing medications indicate only modest reductions in MS fatigue.[23] However, non-pharmacological strategies may be effective in reducing the impact of MS fatigue on daily activities.[24–28] In fact, meta-analyses indicate that self-management interventions might be more effective than medications in reducing the impact of MS fatigue.[29] Fatigue self-management interventions aim to empower people to learn skills and behaviours that maximise available energy.

Several studies have shown that fatigue self-management interventions might be effective in reducing the impact of fatigue. These interventions have used a wide-range of approaches and delivery formats to promote skill acquisition and behaviour change. Interventions approaches have included using cognitive–behavioural therapy, promoting physical activity, and encouraging energy management strategies, such as activity pacing, re-evaluating priorities, communicating needs and reorganising spaces.[24–28 30–36] One of the most frequently studied fatigue self-management interventions is the '*Managing Fatigue: A 6 week energy conservation intervention*'.[37] *Managing Fatigue* was originally delivered in a face-to-face group format, but has been adapted and tested in many delivery-formats. Teleconference, internet and one to one, in-person delivery formats of the *Managing Fatigue* intervention may all be effective in decreasing the impact of fatigue and improving health-related quality of life in people with MS.[24–28] Comparing outcomes immediately before to 1 year after the *Managing Fatigue* intervention indicate that the beneficial effects might be maintained.[26] The *Managing Fatigue* intervention is client centred, primarily focused on encouraging energy management strategies, and is typically facilitated by an occupational therapist (OT). The intervention can increase self-efficacy and engagement in fatigue self-management behaviours, which in turn reduces the impact of MS fatigue.[24–28]

Although the *Managing Fatigue* intervention is effective on average, heterogeneity exists among participants' responsiveness to the intervention.[38–40] The effectiveness of the *Managing Fatigue* intervention may depend on the fidelity of delivery (eg, delivering all sessions and activities). Some studies have found adapted versions (eg, not all sessions or homework activities were assigned) of the *Managing Fatigue* intervention to be ineffective or that benefits were not maintained at long-term follow-up.[30–32] There are some indications that disease characteristics, comorbidities, demographic characteristics and environmental circumstances may influence the effectiveness of the *Managing Fatigue* intervention.[38–40]

To understand why differences in responsiveness to this and potentially other fatigue self-management interventions exist, comparative effectiveness research is needed. Comparative effectiveness research can be used to identify how to better tailor the intervention, so it is more effective for all. For example, comparing different ways of delivering the *Managing Fatigue* intervention can help reveal the active ingredients of the intervention and identify who benefits more from which delivery format. Such knowledge can be used to avoid adapting the intervention in ways that reduce its effectiveness and help better tailor the intervention to improve outcomes.

Knowledge of the effectiveness of the different delivery formats also has the potential to improve dissemination and equity of access to care. Many people with MS have difficulty accessing in-person clinical services to learn about fatigue self-management behaviours.[41 42] Remote-delivery formats might help improve access to services and require the same or fewer resources to implement.[43 44] However, it is unknown whether remote formats are non-inferior to a traditional in-person clinical format. Such knowledge gaps contribute to hesitation among OTs to deliver services remotely, to reluctance among insurance companies to reimburse for remotely delivered OT services, and to unwillingness among administers to establish and support the necessary infrastructure needed to remotely deliver services.

Thus, the purpose of this non-inferiority study is to compare three modes of delivering the *Managing Fatigue* intervention—two remote delivery formats (teleconference and internet) and one in-person format—regarding perceptions of fatigue and its impact on physical, mental and social function. The primary hypothesis is that teleconference and internet versions of the intervention are non-inferior to the traditional mode of clinical service delivery (ie, one to one, in person) in terms of the primary outcome of self-reported fatigue impact and the secondary outcome of health-related quality of life at 2 months. We are also examining whether baseline characteristics (ie, disease, sociodemographic and psychosocial characteristics) moderate outcomes of the *Managing Fatigue* intervention and whether changes in self-efficacy and fatigue self-management behaviours mediate changes in outcomes.

## METHOD AND ANALYSIS

### Study design

We are conducting the first randomised clinical trial to directly compare three delivery formats of the *Managing Fatigue* intervention. We are using a pragmatic design approach in which 582 participants with MS are being recruited and randomised to teleconference, internet or in-person versions of the intervention led by a licensed OT. All versions contain the same intervention content but are presented in ways most appropriate to the delivery format. Our goal is to recruit a diverse research sample to examine the effectiveness of each delivery format on different subgroups of participants (ie, disease, demographic and psychosocial characteristics). Outcomes are being measured at baseline, 2 months, 3 months and 6 months. To help facilitate recruitment, the study is being branded as REducing Fatigue and Restoring Energy to Support Health (REFRESH).

### Sample size and inferiority margin

A sample size of 582 participants is needed to achieve a power of 0.90 for testing the hypothesis and conducting the moderation analyses. Based on previous studies and to err on the side of being conservative, we assumed an attrition rate of 35%, a standardised mean difference of 0.3, a correlation of 0.45 (rho) and a two-sided alpha level of 0.05.[45] An interaction-to-overall effects ratio estimated the extra number of participants needed to examine interactions between delivery formats and participants' baseline characteristics.[46] The prespecified inferiority margin is 10 points, which is based on triangulating anchor-based and distribution-based methods to calculate the minimally important difference (MID) on the Fatigue Impact Scale (FIS), and is consistent with a standardised mean difference of 0.3.[47–49]

### Recruitment and eligibility

The primary recruitment method is community outreach in the Midwestern and Northeastern United States, involving four approaches: (1) advertising with non-profit organisations (eg, visiting support groups and going to events), (2) using social media (eg, Facebook), (3) asking neurologists and rehabilitation professionals to provide flyers to their patients, and (4) engaging community stakeholders (eg, snowballing recruitment). Inclusion criteria are a self-reported diagnosis of MS, at least 18 years of age, moderate-to-severe fatigue (ie, Fatigue Severity scale score ≥4),[50] and ability to speak and read English (ie, confirmed via phone conversation and self-report). Exclusion criteria are the inability to understand the consent form (eg, assessed with five questions about the study) or the inability to participate in the intervention (eg, unwilling or unable to travel outside the home).

Several steps are being taken to ensure that those who meet the study criteria have the opportunity to participate in the intervention: for example, providing transportation to in-person visits and providing participants with a Chromebook to access the internet intervention if needed. Universal Design Principles for research are also being implemented,[51] for example, recruiting participants through various media (ie, print, audio and in person), providing multiple options to express interest in the study and complete questionnaires (eg, paper and pencil, internet and phone), and implementing strategies to include people with low vision (eg, making reading material available in large print and audio formats and enabling text-to-speech functionality). Because of the pragmatic design approach, we are monitoring but not excluding participants for receiving other treatments for fatigue or participating in other rehabilitation services before or during the study. Participants are permitted to withdraw from the study at any time for any reason. Reasons for withdrawal and inability to participate in the intervention are being documented and will be examined in sensitivity analyses.

### Randomisation and allocation concealment

Each participant will be randomised to receive one of the three interventions. Participants are randomised only after availability is confirmed for each delivery format, baseline data collection is complete and there are enough participants within a specific geographic region (18–30 participants) to conduct the group sessions. Permuted block randomisation is being implemented. A statistician, who is not involved with data collection or participant interactions, developed a random number table using a 1:1:1 allocation ratio in blocks of 6. The statistician directly imported the table into the Research Electronic Data Capture (REDCap)[52] system to conceal group assignment. REDCap reveals group assignment only after all baseline data are collected and verified by the project manager. Participants are permitted to switch group assignment only when we are unable to provide services (eg, an OT becomes sick and is no longer able to deliver services or a participant is unable to use a computer).

### Masking

As in most behavioural and rehabilitation interventions, direct interaction between participants and OTs is required, making complete masking impossible. To mitigate bias, each OT is delivering only one intervention format, that is, teleconference, internet or one to one. Data collectors are being masked to group assignment to minimise any biases in baseline or follow-up data collection. We are also measuring the expectations of benefits for each delivery format and conducting sensitivity analyses on measures of treatment fidelity. The study is being described to participants as a comparison of three courses that could all be equally beneficial for reducing the impact of fatigue.

### Intervention procedures

Teleconference, internet and in-person delivery of the *Managing Fatigue* intervention are being compared because of their contrasting advantages and disadvantages, the useful information provided to stakeholders and prior

evidence that this intervention is effective in reducing fatigue impact compared with waitlist controls.[24–28] The reference group is the one to one, in-person format because it is consistent with clinical practice and the input we received from stakeholders about the need to show remote delivery formats are as effective as in-person formats. The comparison groups are the internet and teleconference formats because of the potential advantages of delivering the intervention remotely. Regardless of delivery format, the following six topics will be covered during the intervention: (1) importance of rest and sleep, (2) communication and body mechanics, (3) activity stations, (4) priorities and standards, (5) balancing your schedule and (6) course review and future plans. Participants receive information on taking rest breaks, re-evaluating priorities, communicating needs and reorganising spaces. Practice activities involve experimenting with strategies for 'banking' energy and 'spending' limited energy to meet personal, meaningful goals. Participants are supported to test and tailor fatigue self-management strategies as appropriate to their own situations. Strategies to manage sleep difficulties and cognitive fatigue, not included in the original intervention, are incorporated into all three delivery formats for this study based on their prevalence and severity among people with MS.[53 54]

### Teleconference

This 6-week, group-based intervention involves weekly 80 min teleconference sessions (ie, phone only). Group sizes are kept small (5–10 participants) to maximise participants' opportunities for interaction. Participants receive a programme manual divided into six sections, one for each week, that includes worksheets and practice activities for participants to apply what they learn. Participants have the option of receiving the manual via email or mail. On the designated date and time, participants and the OT dial a toll-free conference call line. If a participant misses a session, research staff will call them to provide an abbreviated summary of the session.

### Internet

Similar to the teleconference intervention, the internet intervention lasts for 6 weeks and is group based; however, unlike the teleconference intervention, participation is asynchronous, with participants able to log on whenever convenient for them. As per the teleconference programme, 5–10 participants start the intervention at the same time and interact during the intervention, also facilitated by an OT. Participants are given a username and a password to view the intervention content via a secure website. Each week, a new session is activated. Each session includes content delivered via text and short videos, completion of interactive activities and information sharing. OTs facilitate the group discussion boards by responding to entries, asking questions and prompting discussion, and providing encouragement. Website content can be downloaded by participants who wish to have paper copies. To ensure that all participants are able to access and navigate the site, a welcome week session is delivered prior to the first session. However, no intervention content is delivered during this session.

### One to one, in person

Unlike the teleconference and internet interventions, the number and length of sessions for the one-to-one, in-person intervention vary over the 6-week period. The OT delivers all six topics, but the pace is tailored to participants' needs and preferences. Thus, although the topics are consistent, OTs can spend more time on those topics that participants find most relevant to them. The participants and OT are instructed to meet at least three times, with at least 7 days between sessions. Similar to the teleconference, participants receive a programme manual divided into six sections. Sessions are held at a central location or at participants' homes on a day and time convenient for both the OTs and the participants.

## Ensuring the fidelity of the interventions

Bellg *et al*'s[55] recommendation to monitor all aspects of treatment fidelity are being followed. Our goal is to strike a balance between delivering each format consistently, capitalising on the unique features of each delivery format and providing OTs with flexibility to deliver the intervention in a way that meets the participants' needs. This balance is needed to maintain internal validity while helping ensure the generalisability of the intervention when implemented under usual circumstances.

### Theory fidelity

The *Managing Fatigue* intervention is congruent with Social Cognitive Theory[56] and supports increasing self-efficacy to promote engagement in fatigue self-management behaviours. Self-efficacy[57] and fatigue self-management behaviours[58] are being measured and will be tested for mediation. All three interventions are expected to increase self-efficacy and encourage engagement in self-management behaviours. Each delivery format includes strategies to address emotional states, promote social persuasion, practice and master skills, and provide opportunities for peer modelling. However, each delivery format implements these strategies in a different way. For example, each format uses a different approach for eliciting social persuasion and peer modelling: the internet format uses discussion boards and written testimonials from people with MS; the one-to-one format involves in-person interactions with a clinician and the review of written testimonials from people with MS; and the teleconference format involves group interactions among peers and clinicians. It is unknown whether these different ways of eliciting social persuasion and peer modelling influence changes in self-efficacy and behaviour. Thus, the proposed mediation analysis might have broader implications for understanding the 'active ingredients' of interventions and whether their delivery format influences self-efficacy, behavioural change and the impact of fatigue.

### Training of OTs

Multiple OTs in each state are being hired to deliver the intervention over the duration of the study. Consistent with a pragmatic research design, licensed OTs, regardless of experience level, are being hired. However, all OTs receive training to deliver the intervention consistently and as intended. Training is composed of four online sessions about (1) study procedures (part one), (2) MS and fatigue, (3) study procedures (part two), (4) theoretical underpinnings of *Managing Fatigue* and (5) the specific format assigned to deliver. Proficiency is documented using quizzes. OTs also receive ongoing training during the study for the specific format they are delivering. Digital recordings of teleconference and in-person sessions and data on therapist internet activity, along with a review of notes (see below), are used to provide the OTs with feedback.

### Implementation fidelity

In addition to the training, each OT is provided with an intervention manual (or internet site) to facilitate the consistent delivery of the intervention as intended. OTs are asked to use checklists during the sessions (teleconferences and one to ones) and to write notes (ie, clinical impressions) each week. The notes are standardised using a Subjective, Objective, Assessment, and Plan (S.O.A.P.) format and include instructions to document the amount of time spent on each topic, a summary of the interactions, and participants' questions and concerns. Digital recordings of teleconferences and in-person sessions and data on OTs' internet activity are being used to examine whether the course is being delivered consistently and as intended.

### Receipt and enactment fidelity

The extent to which participants participate in the interventions and the extent to which participants enact recommendations are being documented. This includes documenting attendance, participants' level of involvement using the S.O.A.P. format, and the number of internet logins and webpages visited. Enactment is being examined with a validated questionnaire on fatigue self-management behaviours.[58] Quizzes adapted from a previous study are being used to measure understanding and retention of intervention material at 2 months.[25]

## Outcome measures

Primary and secondary outcomes are being collected using the survey function in REDCap. Participants can request a phone interview from research staff masked to intervention assignment and/or a paper and pencil version mailed to their homes if they are unable to complete the surveys in REDCap. The primary outcome is the FIS;[59] the secondary outcome is the Multiple Sclerosis Impact Scale;[60] and the tertiary outcome is the Community Participation Indicators.[61] These questionnaires are valid and reliable for people with MS.[59–62] The primary outcome has been shown to be responsive in previous comparable trials of the *Managing Fatigue* intervention.[24–28 32] Primary and secondary questionnaires account for a wide range of daily activities and social situations impacted by fatigue and results from anchored-based and distribution-based analyses can be used to establish meaningful changes.[59–61 63–65] Potential mediators, moderators and other covariates and possible confounders, as well as time points of administration, are listed in table 1. Plans to reduce missing outcome data and avoid attrition include providing monetary incentives (US$20 for completion of questionnaires at each time point), using multiple methods to engage participants (eg, newsletters, email, text messages and phone calls), and addressing questions and concerns promptly.

## Data management and analysis

Participants expressing interest in the study will first be screened over the phone by research staff using a script in REDCap. Participants meeting study criteria will then be scheduled for an in-person baseline visit. Participants have the option of undergoing the informed consent over the phone or during the in-person baseline visit. At the baseline visit, trained research staff who are masked to group assignment will administer the MS Functional Composite. Baseline visits are typically held in private conference rooms in hotels or libraries in the communities where participants live. Once enough participants in a specific geographical region complete the baseline visit and indicate their availability, they are asked to complete baseline questionnaires via REDCap, phone or mail. Research staff masked to group assignment are available to address questions and enter in data received by phone or mail. Once the questionnaires are completed, participants are then randomised by the project manager.

REDCap[52] is being used to organise research operations, conceal randomisation, track data generation, securely collect data, help ensure consistent research procedures and score questionnaires in real time. At each time point, questionnaires on anxiety, depression, exacerbations, falls and injuries are being used to monitor for adverse events. REDCap automatically notifies research staff when a possible adverse event has occurred based on participants' responses to questionnaires (eg, increases in symptoms of depression or anxiety or worsen of symptoms indicative of an exacerbation). OTs are also provided with instructions to notify the research office immediately if they suspect an adverse event. The participant's physician is informed when additional services are needed for the treatment of an adverse event. Because it is unlikely that these adverse events will be related to the study protocol, an independent Data and Safety Monitoring Board is not being used. If a serious adverse event is related to the protocol, the Institutional Review Board and study sponsor will be notified immediately. Quality control checks (eg, data generation and attrition rate) will occur throughout the study (ie, every few months) by research staff not involved in data collection or delivery of the intervention. Concerns about adverse events or

**Table 1** Schedule of enrolment, interventions and assessments

| | Study period | | | | | |
|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Interventions | Post allocation | | |
| **Timepoint*** | $-t_1$ | 0 | | $t_1$ | $t_2$ | $t_3$ |
| Enrollment | | | | | | |
| Eligibility screen | X | | | | | |
| Informed consent | X | | | | | |
| In-person assessment | X | | | | | |
| Return baseline questionnaire packet | X | | | | | |
| Allocation | | X | | | | |
| Managing fatigue Intervention | | | | | | |
| One-to-one, in-person | | | ◆——— | | | |
| Internet | | | ◆——— | | | |
| Teleconference | | | ◆——— | | | |
| Primary outcome | | | | | | |
| Fatigue Impact Scale[59] | X | | | X | X | X |
| Secondary outcomes | | | | | | |
| Multiple Sclerosis Impact Scale[60] | X | | | X | X | X |
| Community Participation Indicators[61 65] | X | | | X | X | X |
| Moderators | | | | | | |
| Multiple Sclerosis Functional Composite[69] | X | | | | | |
| Medical Term Recognition Test[70] | X | | | | | |
| Neuro-QOL—Anxiety[71] | X | | | X | X | X |
| Neuro-QOL—Sleep[71] | X | | | X | X | X |
| Patient Health Questionnaire–8[72] | X | | | X | X | X |
| Patient Activation Measure[73] | X | | | | | X |
| Craig Hospital Inventory of Environmental Factors[74] | X | | | | | |
| Demographics (ie, urban/rural and race) | X | | | | | |
| Self-report Comorbidity Questionnaire[75] | X | | | | | |
| Modified Social Support Survey[76] | X | | | | | X |
| Mediators | | | | | | |
| Energy Conservation Strategies Survey[58] | X | | | X | X | X |
| Self-Efficacy for Performing Energy Conservation Strategies Assessment[57] | X | | | X | X | X |
| Chronic Disease Self-management Scale[77] | X | | | X | X | X |
| Covariates and possible confounders | | | | | | |
| Sociodemographic (eg, age, gender, income, education, living arrangements and employment) | X | | | | | |
| Godin Leisure-Time Exercise Questionnaire[78] | X | | | X | X | X |
| Adverse events (eg, exacerbations[79] and injuries) | X | | | X | X | X |

Continued

Table 1 Continued

| | Study period | | | | | |
|---|---|---|---|---|---|---|
| | Enrolment | Allocation | Interventions | Post allocation | | |
| Timepoint* | $-t_1$ | 0 | | $t_1$ | $t_2$ | $t_3$ |
| Health and wellness services[80] (eg, occupational therapy, counselling and prescribed medications) | X | | | | | X |
| Expectation of benefits/past experience/ quizzes | X | | | X | | |
| Satisfaction survey (open-ended and close-ended questions) | | | | X | | |
| Symptoms of MS Scale[81] | X | | | X | X | X |
| Neuropsychological Screening Questionnaire[82] | X | | | | | |

*Key: $t_1$=2 months; $t_2$=3 months; $t_3$=6 months.

quality control checks will be discussed in the monthly team meetings and conveyed to other stakeholder groups convened during the study, including people with MS.

Data will be downloaded from REDCap into a statistical software programme. Linear mixed effects model will serve as the primary analysis tool for examining the differential effects of the intervention delivery format on outcomes. The models will include the group assignment variable, time and interaction of time and group, as well as the subject-specific random intercept and slope for accounting for individual heterogeneity. Using the fitted model, the trajectory of outcomes will be plotted over the study period. Direct estimates of the treatment effect at specific times will be derived by specifying the least squares means for the Treatment × Time interaction. Non-inferiority will be established with a 95% CI using the prespecified margin of inferiority at each time point, which is set at 10 points on the total composite score of the FIS. The prespecified inferiority margin for the Multiple Sclerosis Impact Scale is set at eight points for the physical function subscale and six points for the psychological function subscale. These margins are based on anchored-based methods calculated from previous studies.[63 64]

The purpose of the moderator analysis will be to examine the consistency of the intervention's effect across the following subgroups: (1) disability status (ie, people with moderate-to-severe disabilities vs people with mild impairments), (2) race (ie, Hispanic and non-whites vs non-Hispanic whites), (3) environment (ie, people living in rural areas vs urban areas), and (4) psychosocial characteristics (ie, people experiencing societal barriers, depression, low health literacy, low social support and/or low patient activation vs people without these characteristics). This analysis will involve adding an additional interaction term of group × time × characteristic and the two-way interaction term of time × characteristic and group × characteristic using the mixed effects model that will be used to detect the main treatment effects on fatigue impact.

The purpose of the mediator analysis will be to examine whether changes in self-efficacy and fatigue self-management behaviours influence the relationship between the interventions and outcomes. Significant changes across time in self-efficacy and fatigue self-management behaviours will be evaluated using the proposed mixed effects analysis. Following Hayes *et al*,[66] the mediation analysis will involve a series of regression analyses to quantify mediation effects using bias-corrected bootstrapped 95% CI.

We will conduct analyses using both intention-to-treat and per-protocol principles. When using intention-to-treat principles, the treatment of missing values will depend on the type of missingness. In the case of missing at random, the proposed mixed effects models should be sufficient. In the case of missing not at random or non-ignorable, a Bayesian method to jointly model response data and missing data will be applied. When using per-protocol principles, participants who provide complete data and receive four or more intervention sessions will be included in the analysis.

A series of sensitivity analyses are planned to explore how various assumptions and potential confounders might influence the results. Four prespecified sensitivity analyses are planned: (1) significant differences in time-varying factors between groups after randomisation (eg, exacerbations, changes in medications, or changes in health and wellness services), (2) assumptions of missing data, (3) differences in prespecified margins, and (4) treatment fidelity measures (eg, attendance, quizzes and experience of OT). We plan to examine these factors by comparing adjusted to non-adjusted models. Significant differences in time-varying factors between groups after randomisation will be entered into the model as covariates during hypothesis testing. We will examine whether any differences exist in results based on how missing data are treated (eg, missing at random vs missing not at random). We will also use prespecified margins of 4.8

(ie, SE of measurement), 15.5 (the mean of 12 anchored-based MIDs) and 20 (upper limit of the triangulated anchored and distribution-based MIDs). Last, we will assess whether measures of treatment fidelity, such as OT experience and participants' understanding of material, influence outcomes as well as whether differences exist in the per-protocol analysis when participants who provide complete data and attend all six intervention sessions (compared with four and five of the six sessions) are only included in the analysis.

## PUBLIC AND PATIENT INVOLVEMENT

Stakeholder groups comprising individuals with MS, policy advocates, insurance representatives, clinicians and researchers on the project are informing all aspects of the study. This includes drafting and reviewing recruitment and intervention material, branding of the study, selecting which delivery formats to examine, assessing and finding both the ease and length of completing the online questionnaires as acceptable, examining policies and procedure for participant interactions, reviewing the informed consent process, and providing firsthand testimonies about the impact of fatigue and ways to reduce it. Eliciting opinions from stakeholders and encouraging their engagement is being accomplished via multiple approaches, including in-person groups, emails, online surveys, teleconference phone calls and one-to-one, in-person meetings. Multiple approaches are also being used to accommodate various work schedules and obtain diverse stakeholder input (eg, diversity in race/ethnicity, functional status and constituents represented). Stakeholder groups will continue to meet throughout the study to guide the recruitment of a diverse sample, present and disseminate results, and create an infrastructure to support the delivery of the *Managing Fatigue* intervention after the study's completion. The stakeholder groups are chaired by the first author and all major decisions are voted on (eg, selection of interventions and outcomes).

## ETHICS AND DISSEMINATION

The protocol is approved by the Institutional Review Board (IRB, STUDY20180027) at Case Western Reserve University, University of Minnesota, University of Illinois at Chicago, Queen's University, and Dalhousie University. The study is being carried out according to the principles in the Declaration of Helsinki.[67] Eligible participants are being enrolled and randomised into the study only after giving consent to participate. Protocol modifications will be submitted to IRB before being implemented. Research staff will undergo extensive training to properly obtain informed consent. REDCap will be used to securely store data and maintain confidentiality. Study results will be published in peer-reviewed academic journals and presented at local, national and international scientific conferences as possible. We will follow guidelines from the International Committee of Medical Journal Editors to determine authorship.[68] Deidentified datasets and statistical code generated during the study will be made available upon request. We have formed collaborations with several stakeholder organisations that will be involved in the dissemination of the study results. For example, we will conduct clinical in-services, write lay articles to post on social media and publish in magazines with a relevant readership, and meet with advocacy groups, like the National Multiple Sclerosis Society. Participants will also receive a newsletter at the end of the study to inform them about the study results.

## Trial status

Protocol V3.04 (20 September 2019): This RCT was first registered online at ClinicalTrials.GOV in June 2018. The first participant was recruited and randomised in March 2019. Recruitment is expected to continue until March 2021 with 6-month follow-up to be completed in October 2021. Data analysis is expected to be completed in December 2021.

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