Pre-Specified Study Protocol and Statistical Analysis Plan

Original Project Title: Comparing the Effectiveness of Fatigue Management Programs for People with MS

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Method and Analysis

Study Design

We are conducting a randomized 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 randomized 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 (i.e., disease, demographic, and psychosocial characteristics). Outcomes are being measured at baseline, two months, three months, and six months. To help facilitate recruitment, the study is being branded as REFRESH (**RE**ducing **F**atigue and **R**estoring **E**nergy to **S**upport **H**ealth).

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 standardized mean difference of 0.3, a correlation of 0.45 (rho), and a two-sided alpha level of 0.05.[1] An interaction-to-overall effects ratio estimated the extra number of participants needed to examine interactions between delivery formats and participants' baseline characteristics.[2] The prespecified inferiority margin is ten 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 standardized mean difference of 0.3.[3-5]

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 organizations (e.g., visiting support groups and going to events), (2) using social media (e.g., Facebook), (3) asking neurologists and rehabilitation professionals to provide flyers to their patients, and (4) engaging community stakeholders (e.g., snowballing recruitment). Inclusion criteria are a self-reported diagnosis of MS, at least 18 years of age, moderate to severe fatigue (i.e., Fatigue Severity scale score ≥ 4),[6] and ability to speak and read English (i.e., confirmed via phone conversation and self-report). Exclusion criteria are the inability to understand the consent form (e.g., assessed with five questions about the study) or the inability to participate in the intervention (e.g., 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: e.g., 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.[7] For example, recruiting participants through various media (i.e., print, audio, and in-person), providing multiple options to express interest in the study and complete questionnaires (e.g., paper and pencil, internet, and phone), and implementing strategies to include people with low vision (e.g., 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.

Randomization and Allocation Concealment

Each participant will be randomized to receive one of the three interventions. Participants are randomized 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 to 30 participants) to conduct the group sessions. Permuted block randomization 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 six. The statistician directly imported the table into the Research Electronic Data Capture (REDCap)[8] 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 (e.g., 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 behavioral 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, i.e., teleconference, internet, or one-to-one. Data collectors are being masked to group assignment to minimize 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 to wait-list controls.[9-13] 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 re-organizing 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.[14 15]

Teleconference. This six-week, group-based intervention involves weekly 80-minute teleconference sessions (i.e., phone-only). Group sizes are kept small (five to ten participants) to maximize participants' opportunities for interaction. Participants receive a program 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 six 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 program, five to ten 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 six-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 seven days between sessions. Similar to the teleconference, participants receive a program 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[16] recommendation to monitor all aspects of treatment fidelity are being followed. Our goal is to strike a balance between delivering each format consistently, capitalizing 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 generalizability of the intervention when implemented under usual circumstances.

Theory fidelity: The *Managing Fatigue* intervention is congruent with Social Cognitive Theory[17] and supports increasing self-efficacy to promote engagement in fatigue self-management behaviors. Self-efficacy[18] and fatigue self-management behaviors[19] are being measured and will be tested for mediation. All three interventions are expected to increase self-efficacy and encourage engagement in self-management behaviors. Each delivery format includes strategies to address emotional states, promote social persuasion, practice and master skills, and provide opportunities for peer modeling. 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 modeling: 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 modeling influences changes in self-efficacy and behavior. Thus, the proposed mediation analysis might have broader implications for understanding the "active ingredients" of interventions and whether their delivery format influences self-efficacy, behavioral 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), 3) theoretical underpinnings of *Managing Fatigue*, and 4) 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 continuous training and specific 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 (i.e., clinical impressions) each week. The notes are standardized 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 log-ins and webpages visited. Enactment is being examined with a validated questionnaire on fatigue self-management behaviors.[19] Quizzes adapted from a previous study are being used to measure understanding and retention of intervention material at two months.[10]

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[20]; the secondary outcome is the Multiple Sclerosis Impact Scale;[21] and the tertiary outcome is the Community Participation Indicators.[22] These questionnaires are valid and reliable for people with MS.[20-23] The primary outcome has been shown to be responsive in previous comparable trials of the *Managing Fatigue* intervention.[9-13 24] Primary and secondary questionnaires account for a wide range of daily activities and social situations impacted by fatigue and results from anchored- and distribution-based analyses can be used to establish meaningful changes.[20-22 25-27] Potential mediators, moderators, and other covariates and possible confounders, as well as time points of administration, are listed in Table1. Plans to reduce missing outcome data and avoid attrition

include providing monetary incentives ($20 for completion of questionnaires at each time point), using multiple methods to engage participants (e.g., newsletters, email, text messages, and phone calls), and addressing questions and concerns promptly.

<<<Insert Table 1 >>>

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 geographic 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 randomized by the project manager.

REDCap[8] is being used to organize research operations, conceal randomization, 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 (e.g., 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 utilized. If a serious adverse event is related to the protocol, the Institutional Review Board and study sponsor will be notified immediately. Quality control checks (e.g., data generation and attrition rate) will occur throughout the study (i.e., every few months) by the statistician not involved in data collection or delivery of the intervention. Concerns about adverse events or 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 program. 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. Noninferiority will be established with a 95% confidence interval (CI) using the prespecified margin of inferiority at each time point, which is set at ten 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.[25 26]

The purpose of the moderator analysis will be to examine the consistency of the intervention's effect across the following subgroups: (1) disability status (i.e., people with moderate to severe disabilities vs. people with mild impairments, (2) race (i.e., Hispanic and non-whites vs. non-Hispanic whites, (3) environment (i.e., people living in rural areas vs. urban areas), and (4) psychosocial characteristics (i.e., 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 behaviors influence the relationship between the interventions and outcomes. Significant changes across time in self-efficacy and fatigue self-management behaviors will be evaluated using the proposed mixed effects analysis. Following Hayes et al.,[28] 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 attend 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 pre-specified sensitivity analyses are planned: (1) significant differences in time-varying factors between groups after randomization (e.g., 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 (e.g., 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 randomization 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 (e.g., missing at random versus missing not at random). We will also use prespecified margins of 4.8 (i.e., standard error 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 to 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 focus groups, emails, online surveys, teleconference calls, and one-to-one, in-person meetings. Multiple approaches are also being used to accommodate various work schedules and obtain diverse stakeholder input (e.g., diversity in race/ethnicity, functional status, and constituents represented). Stakeholder groups will continue to meet at least once a month 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 upon (e.g., 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.[29] Eligible participants are being enrolled and randomized 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.[30] De-identified datasets and statistical code generated during the study will be made publicly available. We have formed collaborations with several stakeholder organizations 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.

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Trial status

Protocol V3.04 (09/20/2019): This RCT was first registered online at ClinicalTrials.GOV in June, 2018. The first participant was recruited and randomized 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.

Contributors

MAP, TP, KP, VM, SG, FB, and MF designed the study and helped draft the original grant proposal. MAP and TP provided trial leadership. MAP, TP, VM, SG, MF and SA provided methodological expertise. SA also provided statistical and data management expertise. TP, KP, VM, SG, MF, and FB provided clinical expertise. MAP, KP, and VM provided training and supervision to the OTs. VM oversaw delivery of 1-to-1, in-person intervention format. TP and SG oversaw delivery of internet intervention format. KP and MF oversaw delivery of teleconference intervention format. All authors reviewed and approved the final version of this manuscript.

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Conflict of Interest

Dr. Bethoux has financial relationships with pharmaceutical and devices companies outside the submitted work. The other authors declare that they have no potential or actual conflict of interest pertaining to this research study.

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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
ENROLMENT:						
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[20]	X			X	X	X
SECONDARY OUTCOMES:						
Multiple Sclerosis Impact Scale[21]	X			X	X	X
Community Participation Indicators[22 27]	X			X	X	X
MODERATORS						
Multiple Sclerosis Functional Composite[31]	X					
Medical Term Recognition Test[32]	X					
Neuro QOL – Anxiety[33]	X			X	X	X
Neuro QOL – Sleep[33]	X			X	X	X
Patient Health Questionnaire–8[34]	X			X	X	X
Patient Activation Measure[35]	X					X
Craig Hospital Inventory of Environmental Factors[36]	X					
Demographics (i.e., urban/rural and race)	X					
Self-report Comorbidity Questionnaire[37]	X					
Modified Social Support Survey[38]	X					X
MEDIATORS						
Energy Conservation Strategies Survey[19]	X			X	X	X
Self-Efficacy for Performing Energy Conservation Strategies Assessment[18]	X			X	X	X
Chronic Disease Self-management Scale[39]	X			X	X	X
COVARIATES & POSSIBLE CONFOUNDERS						
Sociodemographic (e.g., age, gender, income, education, living arrangements, and employment)	X					
Godin Leisure-Time Exercise Questionnaire[40]	X			X	X	X
Adverse events (e.g., exacerbations[41] and injuries)	X			X	X	X
Health and wellness services[42] (e.g., occupational therapy, counseling, and prescribed medications)	X					X
Expectation of benefits/Past Experience/Quizzes	X			X		
Satisfaction survey (open- and close-ended questions)				X		
Symptoms of MS Scale[43]	X			X	X	X
Neuropsychological Screening Questionnaire[44]	X					

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