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A randomized pragmatic trial of telephone-delivered cognitive behavioral-therapy, modafinil, and combination therapy of both for fatigue in multiple sclerosis: The design of the "COMBO-MS" trial

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ABSTRACT

Background: Fatigue is one of the most common and disabling chronic symptoms in multiple sclerosis (MS). Optimization of available treatments for MS-related fatigue has been stymied by lack of comparative effectiveness research that focuses on real-world treatment delivery methods and potential modification of treatment effect by other chronic MS symptoms or disability level. This report describes the design of a patient centered, comparative effectiveness trial of cognitive behavioral-therapy (CBT), modafinil, and combination therapy of both for fatigue in MS ("COMBO-MS").

Methods: We describe the methods of this pragmatic comparative effectiveness trial that is guided by a team of patient, family, provider, community, and payer stakeholders. Eligible participants with MS and significant fatigue severity are randomly assigned (1:1:1) to received either CBT, modafinil, or a combination of CBT and modafinil for 12 weeks. The primary outcome is change in fatigue impact as measured by the Modified Fatigue Impact Scale (MFIS) at 12 weeks. Secondary outcome measures include ecological momentary assessment (EMA) measures of fatigue intensity, fatigue interference, and fatigability (measured over 7 days' time at baseline and at 12 weeks), and change in MFIS score at 24 weeks.

Projected outcomes: We hypothesize that combination therapy will more effectively ameliorate fatigue severity than either monotherapy, and that heterogeneity of treatment effects will be found based on depression status, presence of known or suspected sleep disorder, and disease severity. Study findings will assist patients, providers, payers, and policy makers to provide more effective care for managing fatigue in MS.

1. Introduction

Multiple sclerosis (MS), a chronic disease characterized by inflammation and damage to the central nervous system, affects approximately one million Americans and is the leading cause of non-traumatic disability among young adults [104,116]. The most prevalent chronic symptom in MS is fatigue, affecting up to 90% of people with MS [59,61,72]. Nearly half of people with MS describe fatigue as their most disabling symptom [8], impacting activities of daily living, social interactions, quality of life, standard of living, and employment [29,30,32,42,61,70,119].

Fatigue remains one of the most difficult MS symptoms to manage. Decisional uncertainly regarding the approach to fatigue management has been fueled by three major research gaps: (1) lack of pragmatic, comparative effectiveness trials to assess available non-pharmacologic and pharmacologic treatments; (2) lack of examination of potential treatment effect modifiers in fatigue intervention trials; and (3) lack of novel, reliable, patient-centered fatigue outcome measures. There is a critical need to identify tailored, patient-centered MS-fatigue management strategies guided by real-world, pragmatic evidence that accounts

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Abbreviations: CBT, cognitive behavioral therapy; EMA, ecological momentary assessment; MS, multiple sclerosis; PCORI, Patient-Centered Outcomes Research Institute; UM, University of Michigan; UW, University of Washington

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for diversity among people with MS.

Existing fatigue interventions include behavioral and pharmacological strategies. Among behavioral treatments, cognitive-behavioral therapy (CBT) promotes effective self-management skills, including adaptive thought processes and behaviors (i.e. "coping skills"), goal-setting and behavioral activation strategies for engaging in valued activities; it has been shown to ameliorate MS fatigue in both placebo- and active comparator-controlled trials [5,6,12,24,90,107,113]. Positive effects of CBT for fatigue have been demonstrated across a number of modes of delivery, including in-person [113], web-based [90], and group-based delivery [107–109]. Telephone-delivered CBT for MS symptom self-management has been shown to be an effective means of expanding access to this treatment [26]. Despite promising evidence that CBT is an effective monotherapy for many with MS, it remains unknown whether combining CBT with other therapies might improve outcomes, which patients respond to CBT, or how CBT compares to medication in ameliorating MS-related fatigue.

Medications are frequently employed to treat MS-related fatigue [48], though no medication is FDA approved for this purpose. Modafinil is a safe, well-tolerated and effective wake-promoting agent that is FDA-approved for the treatment of excessive daytime sleepiness caused by obstructive sleep apnea, shift work disorder, and narcolepsy. Modafinil is one of the most commonly used medications for MS-related fatigue in clinical practice. Although several studies have demonstrated the effectiveness of modafinil for MS-related fatigue [17,80,92], limitations of previous non-pragmatic trials have precluded prescribing recommendations or FDA approval for MS-related fatigue [53,91,98,102]. Consequently, off-label use of modafinil lacks empirical support from sizeable randomized-controlled studies, leading to uncertainly about when it should be used and in which patients. Modafinil has never been directly compared to CBT, studied in combination with CBT, or studied in a pragmatic trial.

The study described here was developed in response to the Patient-Centered Outcomes Research Institute's (PCORI) request for comparative effectiveness research that resolves decisional uncertainty related to treatment selection for symptom management in MS. Specifically, they sought research that "compares two or more treatment options for specific symptoms in people with MS where uncertainty exists [86]." This report describes the rationale, aims, hypotheses, design, and implementation of a pragmatic, randomized comparative effectiveness trial funded by this PCORI comparative effectiveness mechanism, in this case comparing the effectiveness of CBT, modafinil, and combination of both treatments on MS-related fatigue in the context of common potential effect-modifiers (depression, sleep disturbance, and disability level). This trial examines novel patient-centered fatigue measures, and will provide valuable information for clinical practice and policy concerning one of the most disabling MS symptoms.

2. Methods

2.1. Stakeholder engagement

In keeping with the mission and methodology standards of the study sponsor, the Patient-Centered Outcomes Research Institute (PCORI), the COMBO-MS study team is comprised of researchers at both participating institutions, and a group of stakeholders who are distinct from study participants. PCORI promotes active participation of stakeholders from a variety of backgrounds, ranging from patients and caregivers to healthcare providers and policy makers. Stakeholders participate throughout all phases of the research enterprise, from study conception through dissemination of findings [97]. The COMBO-MS stakeholder panel consists of people with MS, family members and partners of people with MS, MS specialist neurologists and clinical staff, payer representatives from Blue Care Network, and individuals from community advocacy groups, including regional and national representatives of the National MS Society. Our stakeholder panel members have been integral partners in the process since the trial's inception. Patient-centered research questions for the study were developed directly from clinician stakeholders' clinical experiences, and feedback from patient and payer stakeholders. Decisions regarding protocol development were made with direct stakeholder input, with consensus stakeholder approval before protocol finalization. The stakeholders and study team members participate in quarterly meetings; these include an annual in-person meeting held at the lead study site (University of Michigan) and three annual telephone/webinar meetings. In these meetings, as well as additional as-needed interactions, stakeholders are involved in shaping decisions on day-to-day study operations, including regulatory issues, participant recruitment strategies, enrollment/retention, adverse events, and treatment adherence. Specific effects that stakeholders have had on the study during the first year included: choosing layout and photos for recruitment materials, helping shape eligibility criteria by making them more broad and inclusive, assisting in choosing a broader range of outcome measures (e.g. addition of social participation measures), and guiding investigators in how to convey information back to study participants (e.g., creation of participant letters to report sleep disorder risk). Stakeholders will also be involved in monitoring study progress, interpretation of study findings, and dissemination and implementation efforts.

2.2. Study design and synopsis

This is a three-group, randomized, pragmatic comparative effectiveness trial to compare the effectiveness of CBT, modafinil, and the combination of both treatments in the management of MS-related fatigue. Study design reflects key features of a pragmatic trial (e.g., best alternative treatment comparator rather than placebo) [31,111] and are aligned with PCORI's (the funder's) guidelines for conducting patient-centered comparative effectiveness research [87]. Eligible consenting adults with MS who endorse chronic problematic fatigue are randomized in a 1:1:1 ratio to receive telephone-based CBT (Group 1: 12 weeks of one-on-one telephone-delivered sessions of CBT; 8 weekly programmatic sessions +2 maintenance sessions), pharmacological treatment with modafinil (Group 2: 100–200 mg once-twice daily as tolerated, for 12 weeks); or combination treatment with CBT and 12 weeks of modafinil (Group 3). Self-report measures of fatigue impact (Modified Fatigue Impact Scale - primary endpoint) and potential effect modifiers (depression, sleep, and MS disability level) are assessed at baseline and at 8-weeks, 12-weeks and 24-weeks. Data are collected at 8 weeks to allow for examination of mid-treatment changes, to provide another opportunity for data collection (in case of late drop-outs or other reasons for missing at 12 weeks), and to allow for exploratory mediational analyses. For additional data on physical activity level, fatigue intensity (numerical self-report scale), and fatigability (the ratio of fatigue intensity to physical activity level), participants also undergo one week of continuous actigraphy monitoring and ecological momentary assessment (EMA) data collection with a wrist-worn accelerometer pre-treatment (baseline) and at 12 weeks, at the end of therapy. For the study scheme and timeline see Fig. 1.

2.3. Study aims

The specific aims and hypotheses are to:

(1) Compare the effectiveness of 3 therapies: CBT monotherapy, modafinil monotherapy, and CBT + modafinil combination therapy on patient-reported fatigue impact (primary outcome), fatigue intensity, and fatigability among fatigued individuals with MS. We hypothesize that combination therapy will more effectively ameliorate fatigue severity than either monotherapy; (2) Test whether depression, sleep disturbances, or MS disability level modify comparative treatment responsiveness across treatment arms in terms of fatigue impact (i.e., heterogeneity of treatment effects). We hypothesize that combination therapy or CBT monotherapy will be more effective than modafinil

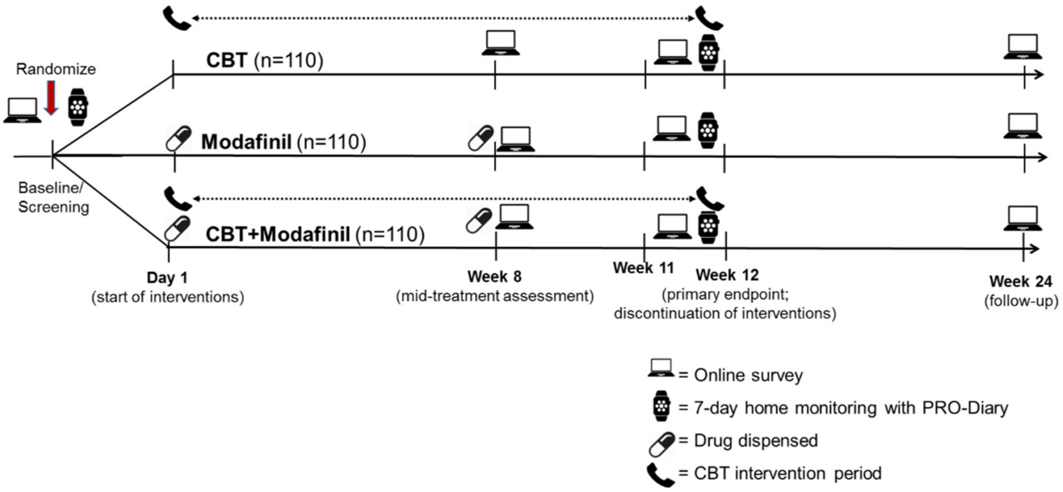

Fig. 1. Study schematic.

monotherapy for those with clinically significant depression, that combination therapy or modafinil monotherapy will be more effective than CBT monotherapy for those with sleep disorders, and combination therapy or modafinil monotherapy will be more effective than CBT monotherapy for those with high levels of MS disability; and (3) Compare adverse events, side effects, treatment adherence, and patient dropout rates among the three treatment arms and patient subgroups of interest. We hypothesize that combination therapy will be associated with higher treatment adherence compared to either monotherapy.

2.4. Study setting

The trial aims to enroll 330 participants across two sites: the UM MS Center at the University of Michigan, Michigan Medicine, Ann Arbor, MI (lead site) and the UW Medicine MS Center at the University of Washington, Seattle, WA. Approximately half of the participants will be enrolled and treated at each site. Assuming a 10% dropout rate, a total of 330 enrollees (165 per site) will yield 100 completers in each study arm.

2.5. Participants' eligibility and recruitment procedures

For this pragmatic trial, inclusion and exclusion criteria were chosen in order to reflect clinical care to the closest extent possible and maximize generalizability such that a broad range of patients with MS-related fatigue would be represented. Inclusion and exclusion criteria are in Table 1.

The University of Michigan (UM) and University of Washington (UW) multiple sclerosis specialty clinics serve as primary recruitment sites. Additional participants are being recruited through UM and UW medical records, other neurology practices throughout Mid- and Southeastern Michigan (by invitation) and the Pacific Northwest, UM and UW electronic clinical trials registries, advertisement through community outlets (e.g., posting flyers in community centers, distributing flyers and fund raising walks), clinicaltrials.gov, Facebook and other social media campaigns, iConquerMS, and from advertisements posted by the NMSS (study stakeholder).

Table 1
Inclusion and exclusion criteria.

Inclusion criteria:
1) Neurologist-confirmed MS diagnosis (all MS subtypes included, regardless of disease duration, disability level, or disease modifying therapy status) 2) Age 18 years or older 3) Presence of chronic, problematic fatigue that, in the opinion of the patient, has interfered with their daily activities for ≥3 months 4) Average Fatigue Severity Scale (FSS) score greater or equal to 4 at screening
Exclusion criteria:
1) Current shift work sleep disorder, or narcolepsy diagnosed with polysomnography and multiple sleep latency test (diagnoses in which modafinil is already widely accepted as symptomatic care) 2) History of MS relapse within the last 30 days prior to screening (participants will be considered eligible after the 30-day window)[*] 3) Current stimulant or wake-promoting agent use such as amantadine (Symmetrel), modafinil (Provigil), short or long acting methylphenidate (Ritalin/Concerta), dextroamphetamine (Dexedrine), dextroamphetamine-amphetamine (Adderall, Adderall XR), lisodexamfetamine (Vyvanse), armodafinil (Nuvigil), or amphetamine (Adzenys XR-ODT, Dyanavel XR, and Evekeo) within 30 days of screening (if present, patients could still be eligible after a 30-day washout) 4) For female participants only: Pregnancy or breastfeeding. 5) For female participants only: Reliance on hormonal contraception (such as birth control pills, shots, implants, patches, vaginal rings, and intrauterine devices) AND concomitant unwillingness to use alternative non-hormonal means of birth control (spermicide or condoms) during the course of the study (modafinil can decrease the effectiveness of oral contraception) 6) Current suicidal ideation (SI) with intent or plan (per a response of ≥1 on the suicide item from the Patient Health Questionnaire-9); these individuals will be assessed by a study psychologist and referred for urgent mental health treatment (people with SI but no intent or plan will be included) 7) Known hypersensitivity to modafinil or armodafinil or its inactive ingredients 8) History of prescription or illicit stimulant abuse (such as cocaine, amphetamine, methamphetamine) 9) History of the following cardiovascular conditions: recent myocardial infarction (last 6 months prior to screening), unstable angina, left ventricular hypertrophy, mitral valve prolapse, NYHA class III or IV congestive heart failure 10) Any other medical, neurological, or psychiatric condition that, in the opinion of the investigators, could affect participant safety or eligibility

[*] The 30-day window was selected based on clinical expertise and published data from numerous MS clinical trials, including those for fatigue, as well pivotal disease modifying therapy trials in which MS relapses are the primary outcome of interest [23,25,38,39,47,63,65].

2.6. Screening and baseline assessments

Initial contact with interested volunteers occurs either over the phone or face-to-face. Individuals who remain interested in participating following a brief description of the study are asked several pre-screening questions to determine appropriateness and timing of an in-person screening/baseline visit. Volunteers who meet all pre-screening requirements undergo a scheduled screening/baseline visit where informed consent is obtained and all inclusion/exclusion criteria are reviewed and confirmed. The participant then completes a battery of web-based self-report and interview-based baseline measures, prior to

Table 2
Major components of the manualized CBT for fatigue management intervention.

Overall treatment goals: Inform participants about fatigue in MS and engage patients to learn and apply fatigue self-management skills tailored to their strengths and priorities. Key skills include: self-monitoring, identifying priorities, goal-setting (based on individual values), energy conservation/self-pacing, behavioral activation, relaxation techniques, sleep behaviors, and managing thoughts and emotions.

Session #	Session content
1	*Introduction to MS-related fatigue and fatigue self-management* Factors that contribute to MS fatigue, self-management philosophy, self-monitoring, relaxation practice.
2	*Goal setting and identifying stressors* Exploring priorities, setting goals, stress response and relaxation, relaxation practice.
3	*Energy management* Energy management strategies/priorities, energy conservation/pacing training, staying active, relaxation practice.
4	*Working with thoughts (part 1)* Identifying/labeling thoughts, distraction, relaxation practice.
5	*Working with thoughts (part 2)* Challenging unhelpful thoughts, evidence gathering, alternative thoughts, relaxation practice.
6	*Sleep* Sleep behavior assessment, education about sleep regulation, establish a plan for healthy sleep hygiene, problem-solving barriers to sleep disturbance, relaxation practice.
7	*Managing stress* Stress, emotions and fatigue, stress management, mindfulness education, relaxation practice.
8	*Building resilience and moving forward* Designing a personal fatigue self-management plan, skills relapse prevention, building resilience.
Maintenance* sessions	Two 15–20 min calls between weeks 8–12, to maintain treatment gains by reviewing and troubleshooting implementation of fatigue self-management skills, including their personal self-management plan.

* Maintenance sessions were optional and used in cases where participants completed the 8 programmatic sessions at least 1 week before the end of the 12-week treatment period.

randomization. Participants are then given a wrist-worn data collection monitor (i.e., the PRO-Diary) and instructions for how to use it during the home monitoring period. Lastly, depending on treatment arm, participants are given instructions regarding modafinil dosing, and/or initiation of CBT. For the purposes of this pragmatic trial, in lieu of a research pharmacy, modafinil is dispensed at a designated clinical pharmacy located at either UM or UW, where participants are instructed to pick their medication up in person, mimicking standard clinical care.

2.7. Study interventions: cognitive behavioral therapy, modafinil, and combination therapy

2.7.1. Cognitive behavioral therapy

Cognitive Behavioral Therapy for fatigue management (CBT; see Table 2), was chosen as a comparator given that previous efficacy studies have demonstrated its benefits in MS [90,113]. For this study, we use one-on-one telephone-delivered CBT for fatigue. In the primary randomized controlled efficacy trial of the telehealth CBT intervention that is the basis for this intervention, 50% of fatigued participants had a clinically meaningful reduction in fatigue impact that was maintained at 6- and 12-months post treatment [27]. The original telehealth CBT treatment protocol focused on multi-symptom management of fatigue, pain, and/or mood. The Ehde et al. [27] therapist manual and participant workbook were adapted for use in this study by decreasing content related to pain and mood and increasing content related fatigue, such as adding more content on sleep, physical activity, and activity pacing. The CBT therapists follow the treatment manual, covering core content for each treatment session. Adherence to delivering core CBT content is assessed through the fidelity rating process (described in detail below). Keeping consistent with this core content, the manualized CBT intervention is tailored to each participant to be responsive to their unique situation (e.g., adaptations to skills practice to account for participant impairments) and to work toward individual fatigue-management goals (identified in Session 2), much like what is done in clinical practice. Participants in CBT are given digital audio recordings of relaxation and mindfulness exercises to facilitate practice of these skills.

All CBT therapists have special training in CBT for symptom management and telehealth delivery and pass a certification procedure to ensure competence in the delivery of the manualized intervention. The team includes two licensed clinical psychologists at each site who supervise the study interventionists that include licensed clinical psychologists, clinical psychology pre-doctoral students or postdoctoral fellows, and Master's level social workers. Therapist training includes readings, didactics, and ongoing review and supervision of recorded sessions. In addition to the CBT supervision conducted at each site, the CBT team engage in group supervision biweekly via videoconference. The fidelity protocol includes therapist manuals, protocol checklists, weekly supervision meetings, and an ongoing independent review of randomly selected digital recordings from at least 10% of all sessions. These procedures ensure that patients assigned to CBT get CBT as prescribed in the treatment manual. If fidelity to treatment is lacking, the therapist receives corrective feedback, additional training, and future sessions are all reviewed to ensure 100% adherence to the protocols.

Often, and similar to clinical practice, 8 weekly sessions of CBT are not possible in 8 weeks due to missed weekly appointment resulting from illness, MS relapses, scheduling errors/conflicts, travel, etc. Therefore, the protocol was set up to ensure that patients could feasibly complete the 8 programmatic sessions within the 12 weeks, even in cases of multiple missed sessions. The maintenance sessions were included for those patients who do successfully complete maintenance sessions well before the end of the 12-week treatment period, in order to maintain any gains they have made as result of the CBT intervention.

2.7.2. Modafinil

Modafinil (2-[(diphenylmethyl) sulfinyl]acetamide) is a centrally-acting oral agent that is FDA-approved to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work disorder. Although the precise mechanism(s) through which modafinil promotes wakefulness remain unknown, the potential benefit of modafinil for fatigue in MS has been demonstrated in 5 previous studies. Three successful open label studies that used various subjective fatigue measures demonstrated a benefit of modafinil on fatigue intensity [17,79,121]. A single-blind placebo-controlled study also demonstrated a significant improvement in fatigue intensity with modafinil [92]. One 8-week, double-blind placebo-controlled trial which examined the effects of modafinil on fatigue intensity showed a significant improvement in fatigue with modafinil [63].

For Group 2 and 3 participants, modafinil is initiated following the 1-week period of baseline actigraphy monitoring. Unlike previous trials, which studied fixed doses of modafinil, our trial includes a flexible dosing schedule, with participants receiving instructions for tailoring the dose according to their needs, as would typically happen in clinical practice.

Modafinil 100 mg tablets are provided. Participants new to modafinil are instructed to start by taking 100 mg of modafinil once daily upon awakening for one week. Depending on perceived response, participants are allowed to increase their dose stepwise to a maximum dose of 200 mg twice daily (upon awakening and around lunchtime, maximum daily dose 400 mg). Alternatively, to lessen known side effects if they arise, participants are allowed to reduce their dose to 50 mg once to twice daily.

For safety, a separate reduced dosing schedule is outlined for participants who are new to modafinil and who have a history of liver problems, participants age 65 or older, participants who use warfarin, phenytoin, MAOIs or cyclosporine, as well as for participants who the investigators think could be at increased risk for sided effects. Participants who meet any of these criteria are advised to initially take 50 mg once daily. Depending on results, participants are allowed to adjust their dose to up to 100 mg once to twice daily (maximum daily dose 200 mg). Participants who were previously on stable doses of modafinil prior to enrollment, without adverse effects, regardless of above criteria, can continue their regular required dose of up to 400 mg per day.

Participants who experience *intolerable* but common side effects associated with modafinil (headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia) that do not fulfill serious adverse event criteria (see below) are required to stop modafinil at the dose which was associated with the symptoms. On a case-by-case basis, upon improvement of symptoms, such participants may be allowed to restart the medication at half of the dose that previously led to prior symptoms. Participants who still continue to experience symptoms after a re-challenge with ½ dose modafinil will be instructed to discontinue modafinil.

2.7.3. Combination therapy

The CBT + modafinil combination therapy will entail simultaneous engagement in both therapies as described above. As with other chronic symptoms, fatigue is a complex problem that may require a multipronged treatment approach for many people. Consistent with this idea, experts in the field have called for the use of combined therapies which include both medication and behavioral (e.g., CBT) interventions to treat MS-related fatigue [21,22,60]. Although data from other chronic health conditions such as major depressive disorder [85,96] and fibromyalgia [4] suggest that combination therapies of both pharmacological and behavioral approaches can have synergistic effects and offer the best chance of long-term success for symptom management [115], such combination treatments for MS fatigue have not yet been tested. This trial seeks to provide needed evidence as to the potential additive effects of CBT plus modafinil on improving MS-related fatigue.

2.7.4. Randomization and procedures to minimize bias

Participants are randomized using a web-based treatment assignment system (http://cscar-randomization.appspot.com/) which was developed and is supported by the UM Center for Consulting for Statistics, Computing, & Analytics Research (CSCAR). This system implements an approach to treatment assignment using minimization methodology that was developed by Pocock and Simon [89]. The minimization approach reduces covariate imbalances by utilizing nonuniform assignment probabilities for the different treatment groups, in order to reduce the level of imbalance following each round of treatment assignment. Randomization parameters set up a priori for this project include equal sampling rates (1:1:1), a determinism of 5, with stratification for MS subtype (relapsing or progressive). MS subtype was included in the minimization procedure (a means of stratifying randomization) given the relatively high proportion of progressive patients at the two academic centers (UM and UW), and prior published data implicating disability as a possible predictor of fatigue in MS (which relates closely to MS subtype) [34,71,94,120].

Only statisticians are blinded for this study. Participants and study team members (PIs, coinvestigators, coordinators) cannot be blinded to treatment assignment. Study participants directly enter outcome data into web-based or ambulatory data collection devices, which eliminate concerns of study staff biases interfering with data collection.

2.8. Data collection procedures and measures

As depicted in Fig. 1, outcomes data are collected at baseline (pretreatment), and 8, 12 (primary endpoint), and 24 weeks after treatment initiation. Patient-reported outcomes are collected in a wrist-worn device (the PRO-Diary, described below) during two 7-day home monitoring periods (baseline and 12 week) and via a web-based data collection platform (REDCap; baseline, 8, 12, and 24 weeks).

2.8.1. The PRO-Diary

The PRO-Diary (CamNTech, Cambridge, UK) is a wrist-worn accelerometer enhanced with a user interface that allows for input of realtime self-reported data. The PRO-Diary is used in this study to provide optimally sensitive assays of fatigue intensity, fatigue impact, physical activity, and fatigability (calculated using fatigue severity and activity measures).

Ratings at wake and bedtime are initiated by the participant upon waking (the time they woke up, not necessarily when they get out of bed) and at bedtime ("lights out" or the time they intend to go to sleep, not necessarily the time they get into bed). An alarm alerts participants to use the touch screen to log symptom ratings at 2 times between 11 am and 7 pm. The PRO-Diary collects physical activity data as 'activity counts' in 15 second epochs during the home monitoring period and stores time-stamped self-report data until the watch is returned to the lab, for data download, cleaning and analysis. The PRO-Diary also generates accelerometer-derived sleep variables, based on physical activity during sleep. These variables include, sleep duration, wake after sleep onset, sleep latency, and sleep efficiency.

Ecological momentary assessment (EMA) provides repeated, realtime assessment of symptoms and functioning in the natural environment, to mitigate recall bias or memory decay. Second, accelerometer technology provides objective measures of physical activity and does not rely on self-report.

2.8.2. REDCap

This study uses REDCap [37,117], a secure, password protected, and HIPAA compliant web-based data platform hosted by the Michigan Institute for Clinical and Health Research (MICHR) at the UM for data capture and storage. This protected database will be accessed and maintained by study personnel only. This system features both a local and remote web-based interface, secure data transfer, and an Oracle database. Data security, patient privacy, and HIPAA requirements are a premium consideration for clinical trials research using REDCap. A complete time-stamped audit of all REDCap activity (including which and when study personnel access data) is maintained, adding to the security and fidelity of the data. Study personnel can enter data into the database through administrative access to add to the self-report data provided by participants. For self-report data collection, participants will access individualized study urls to securely enter data either during clinic visits or at a time of their choosing on an internet-connected device of their choosing (for home-based assessments).

Participant email addresses are used to send the follow-up survey links. Participant emails are stored in REDCap. The UW study staff are

Table 3
Study measures (with time point and data collection method).

Screening measures:
Krupp's Fatigue Severity Scale (FSS) [62]
Patient Health Questionnaire-2 [57,58] plus item 9/i from the PHQ-9 [56] (PHQ-3)

Measure	Pre-treatment baseline	Mid-treatment 8 week	12 week	24 week
Primary outcome				
21-item Modified Fatigue Impact Scale [78]	💻	💻	💻	💻
Secondary outcomes				
EMA Fatigue severity NRS 0-10	⌚	–	⌚	–
EMA Fatigue Severity/Physical Activity (accelerometer)	⌚	–	⌚	–
EMA Fatigue Impact NRS 0-10	⌚	–	⌚	–
Treatment effect modifiers				
National Institute of Neurological Disorders And Stroke Common Data Elements [81]	💻	–	–	–
Self-Reported Expanded Disability Status Scale (SR-EDSS) [14]	🗣	–	–	–
Patient Health Questionnaire-8 (PHQ-8) *Scores ≥ 10 indicate a clinically depressed mood.*	💻	💻	💻	💻
STOP-BANG Questionnaire [19] *Scores ≥ 3 indicate elevated risk for sleep apnea.*	🗣	–	–	–
Insomnia Severity Index [10,73,110,118] *Scores ≥ 15 indicate moderate clinical insomnia.*	💻	💻	💻	💻
RLS Diagnostic Index [13] *Scores ≥ 11 yield 93% sensitivity and 96% specificity to diagnose RLS.*	💻	–	–	–
Epworth Sleepiness Scale [43–46]	💻	💻	💻	💻
Sleep Hygiene Index [68]	💻	💻	💻	💻
EMA Sleep NRS 0–10	⌚	–	⌚	–
Other variables of interest				
Brief Pain Inventory – Short Form Adapted [20,83,84]	💻	💻	💻	💻
Godin Leisure-Time Exercise Questionnaire [35]	💻	💻	💻	💻
PROMIS Self-Efficacy For Managing Symptoms- Short Form 8a [36,66,99]	💻	💻	💻	💻
Quality of Life Subscale-MSQOL-54	💻	💻	💻	💻
PROMIS Cognitive Abilities Short Form 8a [2,11]	💻	💻	💻	💻
Neuro-QoL Ability to Participate in Social Roles and Activities 8 Item Short Form (v1.0) [2,18,33]	💻	💻	💻	💻
Patient Global Impression of Change (PGIC) [41]	–	–	💻	💻
Generalized Anxiety Disorder – 7 (GAD7) [101]	💻	💻	💻	💻
Continuous Accelerometry	⌚	–	⌚	–

Note. ⌚ = 7-day home monitoring with PRO-Diary; 💻 = online self-report survey; 🗣 = interview; PROMIS = Patient Reported Outcomes Measurement Information System; MSQOL = Multiple Sclerosis Quality of Life 54 Instrument; Neuro-QOL = Quality of Life in Neurological Disorders.

only able to view email addresses of UW participants, but as the data coordinating center, the UM study staff has access to email address for all study participants, including those from UW.

2.8.3. *Data transfer (M + Box)*

Transfer of accelerometer/EMA data from the PRO-Diary from UW to the UM data coordinating center is achieved via M + Box - Michigan's implementation of the Box.com cloud storage and collaboration service. M + Box is capable of handling PHI and other sensitive data (e.g., research data). We have used M + Box extensively in previous studies to transfer PRO-Diary data to the lead site for data cleaning and analysis. After it is cleaned and scored, the PRO-Diary data will be later merged with the REDCap data prior to analysis.

2.8.4. *Study measures*

Self-reported measures with evidence for reliability and validity were utilized in this study. See Table 3 for a full list of study measures.

2.9. Data safety and monitoring

To assure adequate protection of the rights of human subjects, per federal regulations (21 CFR 312.50 and 312.53), the study is monitored to ensure that the study is implemented in accordance with the protocol and applicable federal and local regulations, that proper informed consent procedures were followed and to insure the integrity and quality of the data. Per 21 CFR 312.53(d), a qualified trial monitor has been appointed to monitor this multi-site trial in accordance with the protocol and all applicable regulatory requirements. An established monitoring plan was developed to ensure integrity of the data and ensure compliance with Good Clinical Practice.

In addition to the clinical trial monitor, an independent medical monitor is assigned to review adverse events, provide feedback on potential protocol changes, and assist with decisions regarding treatment withdrawal/dose reduction for participant safety.

In regard to the specific issue of suicide risk, participants who demonstrate high suicide risk are excluded from the trial. However, a suicide safety protocol was developed to use with any participant who exhibits indications of possible self-harm at any time during contact with study personnel.

For participants assigned to modafinil, a protocol is in place which defines the rules for treatment discontinuation for safety reasons. These rules include pregnancy, any serious adverse event, onset of severe psychiatric episode (psychosis, severe/uncontrolled depression, or increased suicidality), suspected allergic reactions, and other physical, emotional, or behavioral signs thought to be related to the study treatment. Participants who must have modafinil withdrawn for safety or ineligibility will still be encouraged to stay in the study for observation (and ongoing CBT, for combination treatment group) until completion unless they choose not to continue.

In the event a patient drops out of the study or is lost to follow-up, all attempts will be made to exit the patient in accordance with the protocol requirements. The reason for discontinuation (and the person who decided that discontinuation was necessary) will be recorded.

2.10. Statistical power

For Aim 1 (primary sample size determinant), the 21-item MFIS is the primary outcome variable of interest. The MFIS has been validated in MS patients, is frequently used in MS clinical studies as a reliable measure of fatigue, and is sensitive to changes in intervention [3,26,50,51,64,92,93,102,106]. The primary outcome measure is the mean within-subject difference between baseline and 12-week MFIS values (delta-MFIS), compared between groups. Based on a power analysis of 2-sample means (combined monotherapy groups vs. combination therapy, group weights 2:1), with a 2-sided alpha of 0.05 and standard deviation of 12, a sample size of $n = 300$ subjects will provide 92% power to detect a delta-MFIS of 5 between the monotherapy and combination treatment arms. An MFIS score reduction of 10 is traditionally accepted as a clinically meaningful change in monotherapy trials. Expecting that combination therapy will provide at least 50% greater improvement than the clinically significant difference achieved by either monotherapy (an additional 5-point reduction in the MFIS), the trial has been powered to detect a difference of this magnitude.

Aim 2 analyses focus on effect modification through interaction terms, using fatigue outcomes as the dependent variables (in separate models). Although we expect randomization and stratification by MS subtype to ensure that the majority of variables will be balanced between treatment groups, we conducted a multiple linear regression power analysis to include the majority (up to 11) of possible covariates in the models: age, gender, treatment group (two dummy variables), presence of sleep disturbance (yes/no), depression severity (PHQ-8 Score), disability severity (EDSS score), 3 interaction terms (treatment $*$ sleep, treatment $*$ depression, and treatment $*$ disability), baseline fatigue level, anxiety, pain, and exercise. A similar model will also be constructed using MS subtype and treatment $*$ MS subtype interaction term, (in place of EDSS) to determine if subtype conveys differences in fatigue outcome separate from pure disability measures. Based on a sample size of $n = 300$, including up to 11 predictor variables in the models, we will have 85% power to detect an R-square difference of 0.04 for the interaction terms of interest, assuming the R-squared explained by the adjustment variables is at least 0.3.

For Aim 3, using treatment adherence as the dependent variable (continuous outcome), a multiple linear regression power analysis was performed assuming a full model consisting of up to 8 possible predictor variables: treatment group (independent variable of interest), age, gender, EDSS score, baseline fatigue level, baseline activity level, presence of sleep disturbance (yes/no), and depression severity (PHQ-9 Score). Based on a sample size of $n = 300$, we will have 95% power to detect an R-square difference of 0.03 for the test predictor of interest, assuming the R-squared explained by the adjustment variables is at least 0.3.

2.11. Statistical analysis plan

Aim 1: Compare the effectiveness of 3 therapies: CBT monotherapy, modafinil monotherapy, and CBT + modafinil combination therapy on patient-reported fatigue impact (primary outcome), fatigue intensity, and fatigability among fatigued individuals with MS. The primary outcome measure will be the mean difference in Modified Fatigue Impact Scale (MFIS) score between 12 weeks and baseline (delta-MFIS), compared between treatment groups. A repeated measures mixed effects model will be applied. The mean difference will also be adjusted for baseline covariates: age, gender, anxiety, pain, and exercise, which were included as covariates based on their established association between fatigue and/or activity in MS. Additional secondary analyses will also evaluate treatment effect on EMA outcome measures of fatigue impact, fatigue intensity, and fatigability.

Aim 2: Test whether depression, sleep disturbances, or MS disability level modify comparative treatment responsiveness across treatment arms in terms of fatigue impact. Treatment group effect on fatigue impact scores, fatigue intensity, and fatigability among select subgroups, including those with clinically significant depression, progressive MS subtype and higher EDSS scores, and confirmed/suspected sleep disorders not related to poor sleep hygiene, will be evaluated with interaction terms in mixed effects models as above.

Aim 3: Compare adverse events, side effects, treatment adherence, and patient dropout rates among the three treatment arms and patient subgroups of interest. Descriptive statistics will be used to analyze patterns of adverse events including side effects (incidence, type, severity, and relatedness) and treatment adherence between treatment groups (modafinil vs. CBT vs. combination therapy) throughout the 12-week intervention interval. Adverse event frequency between treatment groups and among subgroups of interest will be evaluated using ANOVA. Multiple linear regression models adjusted for age, gender, EDSS score, baseline fatigue level, baseline activity level, presence of sleep disorder (yes/no), and depression severity (PHQ-8 Score) will be used to determine association between treatment group and treatment adherence (percent usage of prescribed therapy). We also will assess whether degree of treatment effects measured in Aim 1 are related to treatment adherence (e.g. “dose response”).

2.12. Analysis of exploratory aims

Additional repeated measures general linear models will be used to evaluate treatment effect on the difference between 8 week and baseline MFIS scores, to assess whether treatment effects are detectable prior to the 12-week assessment period. Furthermore, we will assess the treatment effect on the difference between 24 week and baseline MFIS scores, to assess whether treatment effects are detectable following the 12-week assessment period. Descriptive statistics will be used to summarize clinical treatment utilization patterns between 12 and 24 weeks, following the 12-week intervention interval.

The treatment effects on other outcomes at 12 and 24 weeks will be assessed. We will examine differential treatment effects on changes in the following factors (assessed via survey): ability to participate in social roles and activities, pain interference, quality of life, and self-efficacy for managing MS symptoms. We will also examine differential treatment effects on changes from baseline to 12 and 24 weeks in the following outcomes that were assessed via survey and/or EMA: pain intensity, perceived cognitive functioning, and pacing behaviors. Treatment group differences in scores on the PGIC measure at 12 and 24 weeks will be examined.

If potential mediators of the treatment effects, such as self-efficacy for managing symptoms [69,112], sleep [112,114], depressed mood, and anxiety [49], show significant changes from baseline to 8 weeks, mediational analyses, either structural equation modeling or mixed effects regression models will be used to test whether the effects of the treatment arms are mediated through common (simple mediational analyses) or different (moderated mediation) mechanisms.

2.13. *Trial status*

The trial was first posted to ClinicalTrials.gov on 08/08/2018 under identifier NCT03621761. Recruitment started in November 2018. The UM Medical Institutional Review Board (IRB) approved the study protocol on 07/05/2018. The UW Human Subjects Division (IRB) approved the study protocol on 09/25/2018. The treatment phase of the study is expected to last until 10/31/2020, with the final follow-up assessments completed by 04/2021.

2.14. *Availability of study data*

This study will be compliant with PCORI's Policy for Data Management and Data Sharing [88], which, at the time of the drafting of this paper, stipulates that awardees deposit the analyzable data set (i.e., data set that is final, cleaned, locked and de-identified in accordance with the HIPAA Privacy Rule (45C.F.R. § 164.514b)), full study protocol, metadata, data dictionary, full statistical analysis plan, and analytic code in a data repository that PCORI designates. Parties seeking access to this study data will be required to request the data through an established review process as outlined in PCORI's policy statement on data sharing [88].

3. Discussion and conclusions

In response to a longstanding gap in knowledge and clinical practice, this study seeks to directly compare three common MS fatigue treatment options used in clinical settings: a medication (modafinil), a nonpharmacologic intervention (cognitive-behavioral therapy), and a combination of the two. This trial offers a critical opportunity to reduce decisional uncertainty and shape clinical practice guidelines and payer policies.

To improve management of fatigue, providers and patients need more information regarding the real-world effectiveness of CBT and modafinil that accounts for the diversity of the MS population, effects of treatment on daily function, and the heterogeneous experience of fatigue. Interestingly, despite a paucity of MS-specific evidence, experts in the field have called for use of combined therapies that include both medication and behavioral (e.g., CBT) interventions [21,22,60]. The reality is that further evidence is needed to increase our understanding of specific patient profiles that may help predict response to specific fatigue treatments, and determine if simultaneous use of behavioral and pharmacological strategies could, in some patients, lead to a synergistic treatment response.

An additional aim is to provide high quality data to inform the payers and policy makers who make decisions about availability and coverage of services. For example, although it is common clinical practice to treat MS-related fatigue with modafinil on an off-label basis, current use and payer coverage is restricted by a lack of guidelines regarding its effectiveness at a population level, as well as by the lack of information on which patient subpopulations should be targeted for treatment. Additionally, although CBT is currently recommended as a first-line treatment for fatigue, current data suggests that barriers such as access to CBT providers and transportation challenges limit its use [100]. Furthermore, although telephone-delivered CBT is increasingly moving into mainstream use, delivery through this modality is not yet common practice on a national scale, particularly for MS fatigue. The proposed trial will impact the expansion of telehealth for treatment of MS-related fatigue by: 1) providing efficacy data that helps to normalize and lend credibility to telehealth within the health care culture; 2) reducing the perception that telehealth requires significant modification to existing treatment approaches; and 3) providing essential information to payers and policy makers who determine coverage of telemedicine on a state-by-state basis.

This trial also seeks to address prior gaps in interventional fatigue research concerning common potential effect modifiers, and in doing so, address decisional uncertainty about which fatigue intervention(s) might be best for a given MS patient. Individual differences in depressive symptoms, sleep, and MS subtype (which is inextricably linked to disability status) need to be examined in clinical trials given their strong associations with fatigue, and potential mechanistic roles in the development and maintenance of fatigue in MS [1,7,9,15,16,21,22,52,60,67,103]. Indeed, there are a number of practical benefits to examining heterogeneity of treatment effects in trials comparing interventions that target distinct contributors to fatigue (e.g. emotional, behavioral, physiological). The current trial includes assessment of heterogeneity of treatment effects for depression, sleep disturbances, and disability level, which will provide clinical information to make better decisions about patient care.

Finally, the study seeks to apply more innovative fatigue measurement methodology to assess the effects of the proposed interventions more completely. The novel measurement methods utilized in this study will provide a better understanding of the day-to-day dynamics of self-management behaviors, symptom occurrence, and functional outcomes, thereby offering a more patient-centered assessment of fatigue treatments for MS. Existing clinical trials for MS fatigue treatments have been restricted to self-reported estimates of symptoms, and functioning experienced within a set retrospective time frame (e.g. pain in the past week). This measurement approach is heavily influenced by recall bias and memory decay for autobiographical information, contributing to a less reliable assessment of symptoms. These issues are especially concerning given that these problems with data fidelity may be exacerbated in MS due to the cognitive problems associated with the condition. Indeed, a recent study showed that a composite of 5 days' worth of self-report ratings was necessary to establish a sufficiently reliable baseline measure of pain intensity in clinical trials [40]; our own data in 108 individuals with MS indicate that fatigue symptoms show more within-person variability (50% within-person variability) compared to pain symptoms (41% within person variability) suggesting the need for a strong repeated-measures fatigue assessment to compare interventions [54]. This trial employs a combination of two novel measurement strategies – ecological momentary assessment and accelerometer technology using the PRO-Diary. Physical activity - a focus of rehabilitation care and CBT interventions- is an important outcome in its own right and is closely linked to self-efficacy for managing MS-related pain, fatigue, mood [76], overall quality of life [74,77,82,95,105], and functional decline [75], and can be used to quantify fatigability in daily life.

Fatigability, which reflects changes in a person's perceived level of fatigue as a result of activity [28], has also emerged as a crucial outcome measure that transcends measures of fatigue intensity or impact to better characterize the patient experience [55]. For example, two people with MS could score similarly on a fatigue intensity measure, but in the context of different lifestyles and levels of daily activity – one person fatigues easily, after very little activity, whereas the other person fatigues only after prolonged, vigorous activity. Thus, fatigue measures that do not reflect fatigue in the context of an activity index do not provide a full picture of how limiting fatigue may be for an individual. This is relevant to comparative effectiveness research, in that it is possible for a fatigue treatment to be deemed "effective" based on its ability to successfully reduce fatigue intensity, yet, may do so by way of reduced activity; the net effect would be that patient function and quality of life would not improve. Conversely, a treatment that fosters increased activity may not necessarily lead to robust reductions in fatigue intensity, and could be deemed ineffective when in fact the net outcome is improved patient functioning. In this sense, use of a fatigability outcome measure, as proposed, could provide a clearer picture of the impact of an intervention on fatigue symptom burden as well as activity and functioning.

Some potential limitations must be acknowledged. Although this is a multicenter study, restriction of study activities to two large academic centers could potentially limit the generalizability. In addition, although efforts were made to minimize participant burden by limiting the number of in-person visits for both assessment and interventions, volunteers must be willing to travel to study sites to participate, so patients from more remote regions who are less willing to travel to an academic medical center may be underrepresented in this study. We did consider the possibility of a placebo arm for the study (and now acknowledge this as a potential limitation), but ultimately did not pursue this route for several reasons. The first relates to the pragmatic nature of the trial and sponsor [31,87,111]. In general, PCORI only considers placebo to be a reasonable comparator "if active treatments are not available". Our assessment of the evidence for Modafinil is that while there are inconsistencies in the literature regarding its effectiveness, likely due to variability in samples and methods, there are a number of studies that show positive effects and we aimed to address some of the prior methodological limitations of prior negative studies in this protocol. Given the fact that both modafinil and CBT alike have demonstrated utility for fatigue MS in prior trials, as well as the fact that both treatments are already in use in MS clinical practice, our stakeholders were also against the use of a placebo arm.

4. Conclusion

Many individuals with multiple sclerosis (MS) suffer from fatigue, which is often their most disabling symptom. This randomized comparative effectiveness trial, guided by feedback from MS patients, MS providers, community organizations, and payers, help patients, providers, and policy makers determine which patients with fatigue respond best to cognitive behavioral therapy or modafinil, and which MS patients may benefit most from a combination of these treatments.

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Disclaimer

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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