COMBO-MS: Cognitive Behavioral Therapy, Modafinil, or Both for MS Fatigue

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Protocol

Title: A randomized controlled trial of telephone-delivered cognitive behavioral-therapy, modafinil, and combination therapy of both interventions for fatigue in multiple sclerosis

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Institution: University of Michigan

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National Multiple Sclerosis Society

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PROTOCOL SUMMARY

Background and Rationale

This pragmatic RCT aims to compare the benefits and harms of a commonly accepted behavioral strategy (cognitive behavioral therapy, or CBT), a commonly used pharmacological therapy (modafinil) and combination therapy with both treatments for the treatment of fatigue in patients with multiple sclerosis (MS).

Fatigue is one of the most common symptoms of MS, affecting up to 90% of MS patients at some point in their disease course. The majority of persons with MS also describe fatigue as their most disabling symptom, surpassing pain and even physical impairment. Fatigue impacts activities of daily living, social interactions, and quality of life, and has profound socioeconomic consequences, including loss of occupation.

Fatigue also remains one of the most difficult MS symptoms to manage, due to an incomplete understanding of the daily patient experience of fatigue in MS, poor understanding of factors that influence its severity, and lack of evidence regarding how to effectively leverage existing treatments for optimal outcomes. A critical need exists to optimize the use of available therapies for fatigue in MS, and to identify tailored, patient-centered strategies fueled by pragmatic research that accounts for diversity among MS patients.

Both pharmacological and behavioral strategies exist for the treatment of MS fatigue. Among behavioral treatments, cognitive behavioral therapy (CBT) promotes effective self-management skills, including adaptive thought processes and behaviors (i.e. "coping skills"). CBT also commonly teaches goal-setting and behavioral activation strategies for engaging in physical, social, and other valued activities in the context of fatigue. CBT has been shown to ameliorate MS fatigue in both placebo-controlled trials, and in trials that have used active behavioral comparators. CBT for MS symptom self-management has also been adapted for telephone-delivery, effectively expanding access to this treatment. Yet, despite promising evidence that CBT is an effective monotherapy for many individuals with MS, it remains unknown whether combining CBT with other therapies might improve outcomes, particularly for those who do not respond to CBT alone, which patients respond most favorably to CBT, or how CBT compares to pharmacological treatments in ameliorating MS-related fatigue.

Pharmacological approaches are also frequently employed to treat fatigue in MS, yet the effects of these treatments have never been directly compared to CBT, or studied in combination with CBT, or studied in pragmatic trials. Among such therapies, modafinil is a safe, well-tolerated and effective wake-promoting agent that is FDA-approved for the treatment of fatigue related to sleep disorders. Modafinil is also 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 (testing doses up to 400 mg per day), limitations of previous non-pragmatic trials have precluded formal prescribing recommendations or FDA approval of this medication. Consequently, off-label use of this drug is weakly supported in an unofficial capacity, commonly followed by the disclaimer that "larger randomized controlled studies are necessary," leading to decisional uncertainly regarding when it should be used and in which patients.

To address these gaps in our knowledge, this pragmatic RCT will capitalize on a representative, heterogeneous sample of MS patients, novel patient-centered fatigue measures, and expertise from key stakeholders to compare the effectiveness of CBT monotherapy, modafinil monotherapy, and CBT+modafinil combination therapy on fatigue impact, fatigue severity, and fatigability in patients with MS (Aim 1), determine heterogeneity of treatment effects of common potential modifiers including depression, sleep disturbances, and MS disability level (Aim 2), and compare adverse events, treatment adherence, and patient dropout rates among the three treatments (Aim 3).

Objectives, Aims, Endpoints, and Assessments:

The Aims of this randomized, rater-blinded clinical trial are to: 1) Compare the effectiveness of 3 therapies: CBT monotherapy, modafinil monotherapy, and CBT+modafinil combination therapy on patient-reported fatigue impact, fatigue intensity, and fatigability among fatigued individuals with MS; 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); and 3) Compare adverse events, side effects, treatment adherence, and patient dropout rates among the three treatment arms and patient subgroups of interest.

Self-report measures of fatigue impact (Modified Fatigue Impact Scale - primary endpoint), fatigue intensity (Brief Fatigue Inventory) and potential effect modifiers (depression, sleep, and MS subtype/disability level) will be assessed at baseline, at 8-weeks, 12-weeks and 24 weeks. Subjects will also undergo 1 week of continuous actigraphy monitoring and EMA data collection with a wrist-worn accelerometer pre-treatment (baseline) and 12 weeks to collect additional data on physical activity level, fatigue intensity (numerical self-report scale), and fatigability (ratio of EMA fatigue intensity/physical activity level). **See Figure 1, study schematic, Section 3.** Hypotheses to be tested are that, at 12 weeks, treatment with combination therapy will overall lead to greater reductions in fatigue impact, fatigue severity, and fatigability compared to monotherapy, and that comorbid depression, sleep disturbances, and baseline disability level will be important effect modifiers that influence treatment effect and adherence.

Statistical Methods

For Aim 1, 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 the 3 treatment groups. A repeated measures mixed effects model will be applied. Similar models using EMA measures of fatigue impact, fatigue intensity, and fatigability as outcome variables will be used to assess the treatment effect of each group.

For Aim 2, 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. Interactions will be treated as random rather than fixed effects.

For Aim 3, descriptive statistics will be used to analyze patterns of treatment side effects (incidence, type, severity, and relatedness) and treatment adherence between treatment groups (modafinil vs. CBT vs. combination therapy). Adverse event frequency between treatment groups and among subgroups of interest will be evaluated using ANOVA. Multiple linear regression models 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”).

1. INTRODUCTION

1.1 Indication

A critical need exists to optimize the use of available therapies for fatigue in MS, and to identify tailored, patient-centered treatment strategies that accounts for the diversity of MS patients.

1.2 Background and Rationale

Multiple sclerosis (MS) is a chronic, autoimmune disease that causes inflammation and destruction of the brain and spinal cord. This condition is the leading cause of non-traumatic disability among young adults, and affects nearly half a million Americans and 2.5 million people worldwide. In addition to physical disability, MS patients suffer disproportionately from a variety of complications that negatively impact quality of life, including fatigue.

Fatigue is one of the most common symptoms of MS, affecting up to 90% of MS patients at some point in their disease course. The majority of persons with MS also describe fatigue as their most disabling symptom, surpassing pain and even physical impairment. Fatigue impacts activities of daily living, social interactions, and quality of life, and has profound socioeconomic consequences, including loss of occupation. Fatigue also remains one of the most difficult MS symptoms to manage, due to an incomplete understanding of the daily patient experience of fatigue in MS, poor understanding of factors that influence its severity, and lack of evidence regarding how to effectively leverage existing treatments for optimal outcomes.

Despite recent prioritization of personalized medicine, there is insufficient information to guide tailored treatment decision-making for fatigue management in MS. For example, although data from other chronic health conditions such as major depressive disorder and fibromyalgia 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, only single-treatment modalities have been studied for MS fatigue. Furthermore, prior trials of treatments for MS-fatigue have not taken into account specific MS subpopulations who may, by virtue of common comorbidities, respond better to one particular treatment or combination of treatments. Finally, existing trials of some of the most commonly used treatments for MS fatigue have relied on measures that do not fully reflect the patient experience with this symptom. Consequently, clinicians have little evidence to determine whether a specific monotherapy or combination therapy is indicated for a particular patient. Specifically, three major research gaps have contributed to the current decisional uncertainly regarding the approach to fatigue treatment in MS: (1) lack of pragmatic, comparative effectiveness trials, including trials of combination therapies, for two of the most commonly used non-pharmacologic and pharmacologic treatments in clinical practice; (2) lack of assessment of common treatment effect modifiers associated with MS that contribute to fatigue (depression, sleep, and progressive MS/disability severity); and (3) lack of novel, reliable patient-centered fatigue outcome measures.

Among behavioral treatments for MS fatigue, cognitive behavioral therapy (CBT) promotes effective self-management skills, including adaptive thought processes and behaviors (i.e. “coping skills”). CBT also commonly teaches goal-setting and behavioral activation strategies for engaging in physical, social, and other valued activities in the context of fatigue. CBT has been shown to ameliorate MS fatigue in both placebo-controlled trials, and in trials that have used active behavioral comparators such as energy conservation and exercise. CBT for MS symptom self-management has also been adapted for telephone-delivery, effectively expanding access to this treatment. Yet, despite promising evidence that CBT is an effective monotherapy for many individuals with MS, it remains unknown whether combining CBT with other therapies might improve outcomes, particularly for those who do not respond to CBT alone, which patients respond most favorably to CBT, or how CBT compares to pharmacological treatments in ameliorating MS-related fatigue.

Pharmacological approaches are frequently employed to treat fatigue in MS, yet the effects of these treatments have never been directly compared to CBT, studied in combination with CBT, or studied in pragmatic trials. Among pharmacological therapies, modafinil is a safe, well-tolerated and effective wake-promoting agent that is FDA-approved for the treatment of fatigue related to sleep disorders. Modafinil is also 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, the variability and limitations of previous non-pragmatic trials (such as low sample size, lack of evaluation of important effect modifiers, and patient selection issues) have precluded formal prescribing recommendations or FDA approval of this medication. Consequently, off-label use of this drug is weakly supported in an unofficial capacity, commonly followed by the disclaimer that "larger randomized controlled studies are necessary," leading to decisional uncertainly regarding when it should be used.

To inform best practice guidelines and address research these current research gaps, this pragmatic comparative effectiveness RCT aims to compare the effectiveness of cognitive behavioral therapy, modafinil, and combination therapy on MS-related fatigue, in the context of common effect modifiers (depression, sleep disturbance, and disability level), using novel methodology that will capture the day-to-day experiences of patients with MS.

Clinical Rationale

Providers and patients need data 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 heterogeneous experience of fatigue. Experts in the field have called for use of combined therapies that include both medication and self-management (CBT) interventions, but further evidence is needed to determine 1) which patient characteristics determine whether to pursue CBT or modafinil for fatigue; and 2) whether combination therapy with CBT plus modafinil leads to a synergistic response in fatigue management, and if so, which patients are most likely to benefit.

1.3 Safety

Risks

Activities involved with this study will involve no more than a minor increase over minimal risk. There are no alternatives to these data collection procedures. Participants may choose to not participate in any part of this voluntary study. Medical treatment (e.g. medication management) as received as part of routine clinical care will bear no more risk than usual care given the treatment will take place in the same clinical context.

Cognitive Behavioral Therapy phone sessions: **The risks of CBT are minimal**. It is possible that some of the participants may become fatigued during the treatment sessions or find it uncomfortable to talk about their situation with the therapist. Further, given the frequency with which fatigue is associated with psychological distress, as well as the inclusion of people with depression, we anticipate that some of the study participants will exhibit signs of psychological distress during treatment.

The use of telephone sessions will help to reduce the risks related to fatigue. Clinicians will be trained to be attentive to signs of fatigue or distress among all participants, who will be told they can stop any study procedures at any time if they feel uncomfortable. A participant will be referred to a medical professional if a study team member concludes they need attention regarding an acute medical issue as identified in the medical evaluation. All participants will be informed they can stop participation at any time without penalty or any effect on the medical care or benefits they receive at their MS Center (either UM Medical Center or UW Medicine MS Center), or any other medical institution. All participants will be offered the opportunity to discuss any situations or experiences associated with the study procedures they deem uncomfortable or adverse with one of the Principal Investigators or, for UW participants, the UW Site PI or Co-Investigator.

Modafinil: **Use of modafinil involves a minor increase over minimal risk.** Modafinil is generally considered to be safe and well tolerated. The most common adverse reactions (5%) associated with modafinil which occurred more frequently than placebo-treated patients in previous clinical trials were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia. It is recommended that caution be used in patients with a history of psychosis, depression, or mania, to avoid exacerbation of these conditions. Serious rash requiring hospitalization and discontinuation of treatment has rarely been reported. Life-threatening skin conditions such as Steven-Johnson Syndrome or Toxic Epidermal Necrosis Syndrome, angioedema, anaphylaxis, hypersensitivity reactions involving multiple organs, new or increased psychiatric symptoms (including worsening depression, mania, depression, suicidality), or increased blood pressure are possible. Dose reduction is recommended in patients with severe hepatic impairment. Modafinil use may decrease the effectiveness of hormonal contraception, use of alternative or concomitant methods of contraception while taking modafinil and for one month after discontinuation of modafinil treatment is recommended. Elimination of drugs that are substrates for CYP2C19 (e.g., phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by modafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure.

All potential risks of modafinil will be outlined in the informed consent document and discussed with the patient prior to enrollment. Patients will also be advised that there may be unforeseen risks not outlined in the ICF. Based on the package insert, eligibility criteria will exclude pregnant women, and a urine pregnancy test will be required prior to study enrollment. Women of childbearing age will be advised of the risk of decreased effectiveness of hormonal contraception with modafinil use and be advised to use a form of birth control that does not involve hormonal contraception (spermicide or condoms) during the study and for one month after discontinuation of modafinil treatment. Participants with a history of hepatic impairment, participants over age 65, and participants who use warfarin, phenytoin, MAOIs and cyclosporine will be given dose limitations that will not exceed half of the maximal daily dose for healthy patients (50-100 mg once-twice daily as tolerated). Patients will be advised to monitor for common side effects of modafinil including headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia while on modafinil, and if these symptoms occur or worsen, to alert the study team, during which time dose reduction or discontinuation will be discussed. Participants who experience worsening depressive symptoms, psychosis, increased suicidality, or suspected allergic reactions (rash, hives, mouth sores, blisters, swelling of the face, eyes, lips, tongue, or throat, trouble swallowing or breathing, fever, shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine) will be instructed to stop treatment immediately and contact the study team. Participants are also advised not to consume alcohol per the drug label. Participants should be instructed to call study team when new drugs are added or removed from their drug regimens so that drug interactions can be assessed. Participants may choose to discontinue their treatment at any time if they experience any untoward effects that they believe are related to modafinil, but will be encouraged to remain in the study until completion for monitoring. Adverse events and severe adverse events will be assessed/reported regularly and on an as-needed basis in accordance with the protocol, GCP, and IRB standards (see sections 7.5 and 8). Action involving possible PI discontinuation of study drug will be determined promptly in accordance with the protocol, GCP and IRB guidelines, as well as the medical monitor (see section 10 and 13).

Confidentiality (minimal risk): Loss of confidentiality regarding the subject's study data (especially data regarding MS diagnosis and symptoms) could cause embarrassment or have social/occupational consequences. This risk is minimal, because a number of precautions have been taken in order to protect confidentiality. Only authorized members of the research team will have access to study records. All collected data will be entered into a secure password protected electronic database (REDCap) system, which is 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. 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. Data coding will be done by subject ID number. Coded paper records (including ICFs) will be locked in file cabinets, and cross-referenced by a name-subject ID key for verification that will be stored in another location. Identifying information will not be attached to the collected data. Trained study personnel will enter pertinent information into the database. Trained study personnel will enter pertinent information into the database. Computers will be locked when not in use.

Study Questionnaires (minimal risk): Risks of study questionnaire completion include discomfort, frustration, or boredom. These risks will be minimized by allowing participants to complete the majority of their questionnaires from their home computer using REDCap. The process of administering surveys via REDCap is very straightforward; URL links are emailed to study participants, who simply click on the link to complete their survey. They can complete the survey in a single sitting or save and return later to complete it. REDCap provides study personnel with real-time information on what data a participant has provided; in cases where participants do not complete the online surveys in a timely manner reminder calls can be placed.

Ecological momentary assessment (PRO-Diary®, minimal risk): Risks of completing ecological momentary assessments (EMAs) on the PRO-Diary (wrist-worn monitor) include discomfort, frustration, and the potential hassle of interruption of daily routine. These risks will be minimized by allowing participants to initiate the wake- and bed-time assessments when it is convenient for them and by allowing participants to opt-out of or postpone EMAs that are not convenient for them (they will be shown how to silence the monitor/delay reporting). These risks will also be minimized by keeping the assessments as brief as possible. Participants may also experience discomfort from wearing the PRO-Diary®, especially if they are not used to wearing a watch on a daily basis. This risk is extremely rare in our experience collecting data. We will minimize this risk by offering participants choices of wrist band types and by telling them that it may take a few days to get used to wearing the PRO-Diary®.

Suicidal Ideation:
In the event that a participant mentions suicidal ideation or other severe mental distress that could result in harm to self or others, an initial assessment, using the Suicidal Ideation Documentation form will be conducted, by the study team member who is in communication with the participant. Guidelines in this form indicate what the study team member should do in case of a true emergency (i.e. contact emergency services), and how to collect information to adequately assess the participants suicidal risk. One of the study investigators who is a licensed psychologist (Drs. Kratz, Conroy, Ehde, or Alschuler, depending on location) will then be contacted and debriefed on the findings of the assessment. If indicated by the findings of the assessment, one of these psychologists may contact the participant by phone and complete a more in-depth self-harm/suicide assessment, taking appropriate action (e.g. referral for mental health services, contacting emergency services) as needed. All safety related incidents will be reported to the PI and the IRB according to relevant protocols.

As with any research study, there may be additional risks that are unforeseeable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

To compare the effectiveness of cognitive behavioral therapy, modafinil, and combination therapy on MS-related fatigue, in the context of common effect modifiers (depression, sleep disturbance, and disability level), using novel methodology that will capture the day-to-day experiences of patients with MS.

2.2 Endpoints

2.2.1 Primary Outcomes

Fatigue impact, as assessed by:

The mean difference in the Modified Fatigue Impact Scale (MFIS) score between 12 weeks and baseline (delta-MFIS), compared between the 3 treatment groups

2.2.2 Secondary Outcomes

Changes between 12 weeks and baseline in fatigue intensity, fatigue impact, and fatigability (measured using PRO-Diary ecological momentary assessment and accelerometry, measured 4x/day for 7 days, at baseline and 12 weeks), compared between the 3 treatment groups

2.2.3 Exploratory Endpoints

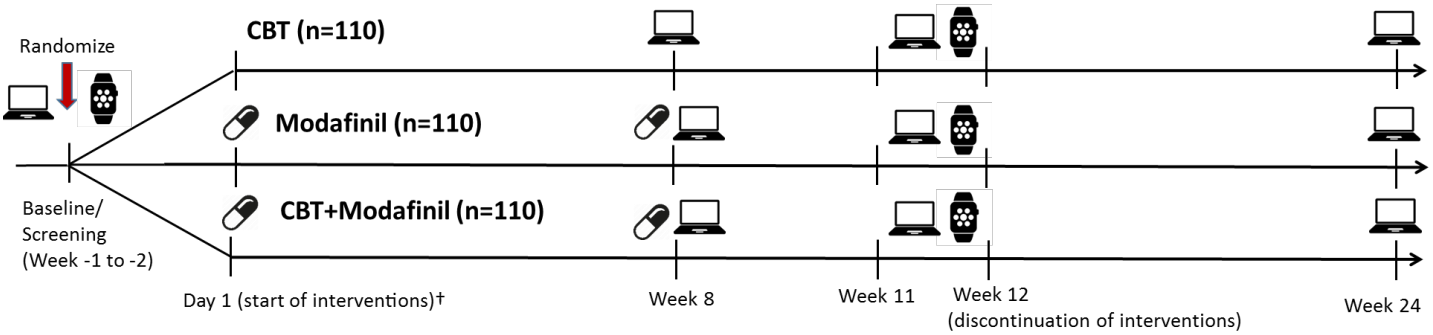
a) The mean difference in the Modified Fatigue Impact Scale (MFIS) score between 0 and 8 weeks, and 0 and 24 weeks (delta-MFIS), compared between the 3 treatment groups

b) clinical treatment patterns post-intervention

3. STUDY DESIGN

This is a randomized, rater blinded, comparative effectiveness trial. Consenting participants with MS and chronic problematic fatigue who meet all inclusion/exclusion criteria will be enrolled and 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 that emphasize fatigue self-management skills; 8 weekly programmatic sessions + 2 maintenance/booster sessions), modafinil (Group 2: 100-200 mg once-twice daily as tolerated, for 12 weeks); or combination treatment with CBT (8 weekly sessions + 2 booster sessions) 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 subtype/disability level) will be assessed at baseline and at 8-weeks, 12-weeks and 24-weeks. Subjects will also undergo 1 week of continuous actigraphy monitoring and EMA data collection with a wrist-worn accelerometer pre-treatment (baseline) and 12 weeks (i.e., concluding at the end of therapy) to collect additional data on physical activity level, fatigue intensity (numerical self-report scale), and fatigability (ratio of EMA fatigue intensity/physical activity level). For specific measures and timeline **see Figure 1, study schematic, below**.



Online surveys
Primary Outcome: Fatigue Impact (*Modified Fatigue Impact Scale*)
Secondary outcome: Fatigue Severity (*Brief Fatigue Inventory*)
Effect Modifiers: Disability Severity (*self-report Expanded Disability Status Scale**)
Sleep disorders (*STOP-BANG*, insomnia severity index, Restless Legs Syndrome Index*, Sleep Hygiene Index*),
Depression (*Patient Health Questionnaire-9*)
Covariates: Demographics*, Anxiety (*Generalized Anxiety Disorder-7*), Pain (*Brief Pain Inventory*), Exercise (*Godin*)
Exploratory (12 weeks post-intervention) Outcomes: Fatigue impact/severity, clinical treatment utilization patterns at 24 weeks

7-day PRO Diary home monitoring
Ecological Momentary Assessment (EMA)
Secondary outcomes: Fatigue Impact (*self-report visual analogue scale),* Fatigue Severity (*self-report visual analogue scale*)
Effect Modifier: Morning assessment of sleep quality (*self-report visual analogue scale*)
Continuous actigraphy
Secondary outcome: Fatigability = ratio of EMA fatigue severity measure/physical activity level
Covariate: Daytime physical activity level

Drug dispense

*assessed at baseline visit only

†marks start of week 1

4. SUBJECT SELECTION

4.0 Subject Recruitment

Participants will be recruited from the UM and UW MS Clinics tertiary clinics. Additional participants will be 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).

The table below shows the current enrollment plan for data collection.

Total number of study participants expected to be screened:	360
Of those screened, total number of study participants expected to be eligible:	340
Of those eligible, total number of study participants enrolled:	330
Target sample size *(i.e., of those eligible, total number of study participants expected to be enrolled)*:	300 completers

We anticipate enrolling 50 subjects per site in year 1, 65 subjects per site in year 2, and 50 per site subjects in year 3, or an average of 4-5 subjects per month per site throughout the course of the study.

4.1 Inclusion Criteria

1. Patients with clinically definite MS (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.
5. Access to the internet with video-capable smart phone or computer if performing study remotely (virtual visit).

4.2 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 (modafinil is contraindicated in these conditions);
5. For female participants only: Reliance on hormonal contraception (such as such as birth control pills, shots, implants, patches, vaginal rings) 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 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
9. Diagnosis of hypertension within the past year not managed by a health care provider
10. Recent history (within 1 year) of prescription or illicit stimulant abuse (such as cocaine, amphetamine, methamphetamine)
11. Any other medical, neurological, or psychiatric condition that, in the opinion of the investigators, could affect participant safety or eligibility.

†Participant behavior or comments that suggest imminent threat will prompt immediate 911 activation. Behavior or comments that suggest SI with plan but no immediate threat will prompt psychiatric ER referral

5. STUDY TREATMENTS

5.1 Allocation to Treatment (see also 6.4)

Randomization Process (see also section 6.3): Participants who meet all Inclusion/Exclusion criteria will be randomized (1:1:1 randomization) to CBT (Group 1, n~100), modafinil (Group 2, n~100), or combination CBT+modafinil after the participant has signed consent and completed the baseline activities.

5.2 Blinding

The subject, PI, co-investigators, interventionists, and coordinators will not be blinded.

5.3 Interventions:

Telephone-based CBT: Cognitive Behavioral Therapy for fatigue (CBT – see table 1), also commonly referred to as "fatigue self-management", was chosen as a comparator given its endorsement in MS fatigue treatment guidelines based on previous efficacy studies demonstrating its benefits in MS. For this study, we will use telephone-delivered CBT for fatigue self-management, which also has a strong evidence-base for its use in MS patients. Developed and tested by one of our study investigators (Dr. Ehde), this treatment is routinely utilized in her clinical practice to manage several chronic symptoms in MS including pain, depression, and fatigue in MS. In her primary trial of this intervention using the telephone-delivered treatment, which targeted MS-related pain and depression as well as fatigue, 50% of fatigued participants with MS had a clinically meaningful reduction in pain impact that was maintained at 6- and 12-months post treatment. This treatment will be delivered one-on-one via telephone by study interventionists with special training in CBT for symptom management and in telehealth delivery. The team of psychologists includes Drs. Kratz, Ehde, Alschuler, and Conroy, who are all licensed clinical psychologists, who will supervise the two study interventionists (one per study site). Study interventionists will be either licensed clinical psychologists, clinical psychology pre-doctoral students or postdoctoral fellows, or Master's level social workers. Currently, the primary interventionists are Kristen Pickup, MSW at UM (Drs. Conroy and Kratz secondary/back-up interventionists) and Jamie Tingey, MSW, Tiara Dillworth, PhD, and Elena Mendoza, MS at UW (Drs. Alshculer and Ehde secondary/back-up interventionists).

The study interventionists will be trained and supervised in the intervention by the study psychologists, including Dr. Ehde (author of the telehealth treatment manual, on which this study is based) and Dr. Alschuler at UW, and Drs. Kratz and Conroy at UM. Training will include readings, didactics, and ongoing review and supervision of recorded sessions. A fidelity protocol will include 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 will ensure therapist fidelity to the CBT treatment (i.e., make certain that patients assigned to CBT get CBT as prescribed in the treatment manual). If poor treatment fidelity is observed, that therapist will receive corrective feedback, additional training, and have all sessions reviewed to ensure 100% adherence to the protocols.

Table 1. Major components of the manualized CBT fatigue self-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 self-management skills include: energy conservation/self-pacing, self-monitoring, sleep behaviors, identifying strengths and priorities, goal-setting (based on individual values), behavioral activation, relaxation techniques, and managing thoughts and emotions.
Session Content (8 weekly sessions and 2 booster sessions; each session 45-60 minutes)
Introduction to MS-related fatigue and fatigue self-management -Factors that contribute to MS fatigue, self-management philosophy, self-monitoring, identifying strengths
Energy management - Self-monitoring check-in, energy management strategies/priorities, energy conservation/pacing training, staying active
Sleep - Sleep behavior assessment, sleep education about sleep regulation, establish a plan for healthy sleep hygiene, problem-solving barriers to sleep disturbance (including morningness/eveningness tendencies); energy management check-in
Goal setting and identifying stressors -Exploring priorities, setting goals, stress response, diaphragmatic breathing (intro to relaxation); energy

management check-in
Working with thoughts (part 1) - Identifying/label thoughts, thought stopping, distraction; relaxation practice; energy management check-in
Working with thoughts (part 2) - Challenging unhelpful thoughts, evidence gathering, alternative thoughts; relaxation practice; energy management check-in
Managing emotions - Emotions and fatigue, living in the present, nurturing positive emotions, gratitude, guided imagery; energy management check-in
Building resilience and moving forward - Designing a personal fatigue self-management plan, skills relapse prevention, building resilience
Two 15-20 minute calls between weeks 8-12, to review and troubleshoot implementation of fatigue self-management skills, including their personal self-management plan.

Modafinil: Modainil will be prescribed by one of the neurologists on the study team. 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. The mechanism(s) through which modafinil promotes wakefulness is unknown. Modafinil's benefits for fatigue in MS have 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. A single-blind placebo-controlled study also demonstrated a significant improvement in fatigue intensity with modafinil in a recent study. 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.

Modafinil will be dispensed for Group 2 and 3 patients following 1 week of baseline actigraphy monitoring and at 8 weeks. At baseline, participants will be prescribed the 100 mg pills (enough to take up to 4 pills per day). They will be advised to take 100 mg once a day (upon awakening) as a starting point for the first week. Depending on results, participants will be allowed to adjust their dose based on the following scenarios:

- If the 100 mg/day dose effectively treats their fatigue throughout the day, participants will remain on this dose.
- If the 100 mg/day dose is adequate, but of insufficient duration, participants will be allowed to take another half pill or full pill around lunchtime (early afternoon: at least 8 hours before bedtime) for a total dose of 150 mg or 200 mg a day.
- If the 100 mg/day dose provides insufficient relief of fatigue, participants may increase the dose to 200 mg/day (upon awakening).
- If the 200 mg/day dose is adequate, but of insufficient duration, participants will be allowed to take another 1 or 2 pills around lunchtime (early afternoon: at least 8 hours before bedtime) for a total dose of 300 mg or 400 mg a day (max dose = 400 mg per day).
- If the 100 mg dose is perceived by the participant to be helpful with fatigue, but associated with excessive side effects (see 1.3), participants will be allowed to decrease their dose to 50 mg, once or twice daily, depending on duration of effect. A pill cutter will be provided by the study team if necessary.

*Participants who report a history of liver problems, participants age 65 or older, participants who use warfarin, phenytoin, MAOIs or cyclosporine†, and participants in whom the investigators think could be at increased risk for side effects, will only be permitted to take ½ of the maximum daily dose, prescribed enough pills to take a maximum of 1 pill twice a day (200 mg/per day) unless they have previously tolerated and required a higher dose prior to enrolling (in which case they will be allowed to return to their previously tolerated dose, up to 400

mg per day) . At baseline, these participants will be prescribed the 100 mg pills. They will be advised to take 50 mg once a day (upon awakening) as a starting point for the first week (A pill cutter will be provided by the study team if necessary.). Depending on results, participants will be allowed to adjust their dose based on the following scenarios:

- If the 50 mg/day dose effectively treats fatigue throughout the day, participants will remain on this dose.
- If the 50 mg/day dose is adequate, but of insufficient duration, participants will be allowed to take another ½ pill around lunchtime (early afternoon: at least 8 hours before bedtime) for a total dose of 50 mg twice a day.
- If the 50 mg/day dose provides insufficient relief of fatigue, participants may increase the dose to 100 mg/day (upon awakening).
- If the 100 mg/day dose is adequate, but wears off more quickly than desired, participants will be allowed to take another half pill or full pill around lunchtime (early afternoon: at least 8 hours before bedtime) for a total dose of 150 mg or 200mg a day (max dose = 200 mg per day).

A medication dispensing log that shows how much drug that was dispensed for each participant at each time point (baseline and week 8) will be used for drug medication review.

†if randomized to a modafinil treatment arm, participants on these medications will be told to inform their prescribing providers of the addition of modafinil to their regimen, to allow the opportunity for additional blood monitoring if the prescriber thinks this is necessary

Combination CBT+modafinil: The CBT+modafinil combination therapy will entail simultaneous engagement in both therapies as described above.

6. STUDY PROCEDURES

Pre-screening: We will be completing record review & pre-screening (over the phone) questions prior to informed consent procedures in order to evaluate initial study eligibility prior to being scheduled for the screening/baseline visit.

6.1 Screening/Baseline Visit

Depending on state or institutional COVID-19 restrictions at time of screening, baseline visits may be conducted virtually (via video meeting) or in-person. Even when in-person visits are permitted, participants will still be given the option for virtual visits.

For in-person visits, subjects will be seen at one of several UM or UW sites for baseline visit activities, including but not limited to the University of Michigan Taubman Neurology Clinic, Michigan Clinical Research Unit (MCRU), and the UW Medicine Multiple Sclerosis Center.

Informed consent will be obtained by qualified study staff. Inclusion and Exclusion Criteria will be reviewed. For virtual visits, the informed consent will be obtained digitally. See section 7.2.4.

The screening portion of this visit will include confirmation of eligibility via:

1) Participant self-report (e.g. FSS, PHQ-3, etc.)
2) Demographic information
3) Focused medical and surgical history as it relates to multiple sclerosis (subtype, prior disease modifying therapy use, disease duration), fatigue, mood disorders and hepatic issues (for modafinil)
4) Medication review

5) Neurologist assessment of eligibility
6) Pregnancy test (For individuals of childbearing age who identify their pregnancy status as unsure)

Eligible subjects will be randomized into one of the 3 study arms & will complete baseline assessments of self-reported fatigue, disability, sleep, exercise, self-efficacy, and other quality of life factors via online Redcap surveys.

6.2 Home monitoring 7-day PRO-Diary application (EMA) – BASELINE AND WEEK 12 ONLY: After completing the above screening/baseline activities, participants will receive instruction on use of the PRO-Diary® accelerometer watch, which the participant will wear during two separate 7-day "home monitoring" periods, at baseline (sent home with watch following baseline visit) and 12 weeks to assess physical activity (objectively measured via accelerometry), AND ecological momentary assessment (EMA) of fatigue intensity, fatigue impact, fatigability (ration of fatigue intensity/accelerometer activity counts), and sleep. **See "Assessments" section.**

The 7-day monitoring period at 12 weeks will take place at the end of the study treatment interval; so that the home monitoring takes place before participants have discontinued their Modafinil, the assessment will begin approximately one week before the end of treatment for all treatment arms (i.e., home monitoring will *conclude* around 12 weeks post-treatment initiation).

6.3 Randomization
Following collection of baseline assessments, participants will be randomized during the baseline screening visit and assigned treatment.

Randomization Process/Blinding: Subjects who meet criteria I/E criteria will be randomized using computer-based randomization via http://cscar-randomization.appspot.com/ (1:1:1 randomization) to determine whether they will receive telephone based CBT monotherapy (Group 1, n~100), Modafinil monotherapy (Group 2, n~100), or combination therapy with both treatments (Group 3). Statisticians and study staff who process data (subjects will enter data directly into the database, so no study personnel are directly collecting data) will remain blinded to group allocation for the duration of the study. The subject, PI, co-investigators, study interventionists, and coordinators will not be blinded.

6.4 Interventions: see also section 5.3
Participants assigned to modafinil or combination therapy will be encouraged to pick up their first supply of modafinil within 7 days of the baseline visit. For virtual visits, participants will receive their first supply of modafinil by mail.

For those who receive CBT or combination therapy will also be able to schedule their first CBT session with the study team during or shortly after this baseline visit.

Participants will be instructed to start their assigned treatment following the 7-day home monitoring period. All treatments will be given for a total of 12 weeks, and treatments will begin after participants complete their first 7-days of PRO-Diary home monitoring.

6.5 Week 8, Week 12, and Week 24 Visits

Group 1 (CBT monotherapy): Participants will have the option of completing all post-baseline REDCap assessments (week 8, 12, and 24) remotely (computer based assessments via weblink which will be provided, or paper forms by mail) or in-person. An internet-connected device will be provided by the study staff member for the participant to complete the REDCap assessments if they choose to complete them during the study visit.

For Week 12 home monitoring period, the watch and instructions for completing the monitoring and for returning the monitor following the 7-day monitoring period (accompanied by a pre-paid return envelope) will be mailed to participants, so that the materials are delivered to the participant ahead of the start of the 11th week. The study staff member will place a reminder call to the participant on or around the first day of the Week 12 home monitoring period and will answer any questions that participant has about completing the Week 12 home monitoring.

Group 2 (Modafinil monotherapy)*: Participants will have the option of completing all REDCap assessments remotely (computer based assessments via weblink which will be provided, or paper forms by mail), or or in-person. An internet-connected device will be provided by the study staff member for the participant to complete the REDCap assessments if they choose to complete them during the study visit. Participants will be able to receive drug refill at 8-week either in-person at UMHS (for in-person visit) or in the mail (for virtual visit). Participants will be encouraged to complete the Week 12 REDCap assessment during the final (12th) week of treatment, as close to the end of treatment as possible. For Week 12 home monitoring period, the PROdiary and instructions for completing the monitoring and for returning the PROdiary following the 7-day monitoring period (accompanied by a pre-paid return envelope) will be mailed to participants, so that the materials are delivered to the participant ahead of the start of the 11th week. The study staff member will place a reminder call to the participant on or around the first day of the Week 12 home monitoring period and will answer any questions that participant has about completing the Week 12 home monitoring. Participants will be asked to report number of remaining modafinil pills at the end of the treatment period and can either bring back any unused modafinil to the study personnel to properly dispose of it, or receive the drug destroyer via mail at the end of the 12-week treatment interval to properly dispose of any unused modafinil.

Group 3 (Combination therapy)*:

Participants will have the option of completing all REDCap assessments remotely (computer based assessments via weblink which will be provided, or paper forms by mail), or in-person. An internet-connected device will be provided by the study staff member for the participant to complete the REDCap assessments if they choose to complete them during the study visit. Participants will be able to receive drug refill at 8-week either in-person at UMHS (for in-person visit) or in the mail (for virtual visit).

Participants will be encouraged to complete the Week 12 REDCap assessment during the final (12th) week of treatment, as close to the end of treatment as possible. For Week 12 home monitoring period, the PROdiary and instructions for completing the monitoring and for returning the PROdiary following the 7-day monitoring period (accompanied by a pre-paid return envelope) will be mailed to participants, so that the materials are delivered to the participant ahead of the start of the 11th week. The study staff member will place a reminder call to the participant on or around the first day of the Week 12 home monitoring period and will answer any questions that participant has about completing the Week 12 home monitoring. Participants will be asked to report number of remaining modafinil pills at the end of the treatment period and can either bring back any unused modafinil to the study personnel to properly dispose of it, or receive the drug destroyer via mail at the end of the 12-week treatment interval to properly dispose of any unused modafinil.

Participants who might be at risk for a sleep disorder (obstructive sleep apnea, restless leg syndrome, excessive daytime sleepiness, and clinical insomnia) which might require further evaluation or treatment based on assessments administered during the study will be notified by letter after their 12-week visit. The letter will recommend that they share the information with their primary care doctor.

6.6 Assessment Windows

Day 1 (start of Week 1) is designated as the point at which treatment starts; this will be somewhere between 7 and 14 days after the baseline visit where randomization occurred. The treatment window is the 12 weeks between Day 1 and the end of Week 12.

Efforts will be made to ensure that assessments are gathered as close to the target assessment time points (Week 8, Week 12, and Week 24) as possible; however, unexpected circumstances often arise that make data collection at very specific time points difficult. Therefore, we have established the following assessment windows. If a participant is not able to complete the assessment during the designated assessment window, they will be allowed to stay in the study (at the site investigator discretion), completing any later assessments as they are able and willing.

Protocol deviations will be completed for participants completing the assessments out of window, with the exception of the prescreening to screening assessment window. Protocol deviations will not be reported for self-report survey data. Self-reported survey data at the baseline, 8 week, 12 week and 24 week surveys is not being collected to assess safety-related information (e.g., side effects, AEs). As is standard, participants are not required to answer any self-reported survey questions they do not wish do answer, and some participants opt to skip questions/surveys they are not comfortable with. If participants skip a question(s) on the surveys (administered online via REDCap), they will be prompted by REDCap that they have missed a question(s) and they can go back and answer or choose to proceed without answering. We have found that in previous studies, skipping questions is rare, and thus we do not expect it to affect data validity.

Additionally, protocol deviations will not be reported for missed EMA assessments administered by the PRO-Diary data during the home monitoring periods. We expect that there may be instances where participants are unable to complete the EMA questions (for example, if it alerts at a time that is inconvenient for them to answer or they forget to answer). Previous studies have shown that compliance with these repeated assessments is ~75%. The EMA assessments do not assess safety so a missed assessment is not a safety concern. We expect that participants will miss some of these assessments and have selected the length of the home monitoring periods (7 days) to make sure data validity is not compromised if participants miss some of the EMA assessments.

Any missed safety assessments will be reported as protocol deviations. Safety assessments are conducted by the coordinator in-person or by phone as applicable under the supervision of the study PIs during the baseline, 8 week, 12 week and 24 week study visits and during any other contact with the participant (e.g., phone calls).

1. Prescreening to Screening/Baseline Assessment Window: Study staff will aim to schedule the screening/baseline visit within 2 weeks of pre-screening. If the baseline visit is beyond 2 weeks from pre-screening, a study staff member will ask prior to the visit if there has been any change (in fatigue, meds, pregnancy, MS relapses, etc.) since pre-screening.
2. Baseline Home Monitoring Assessment Window: Participants will be given 14 days from their Baseline visit to complete their 7-day home monitoring period assessment. Although participants are asked to complete 7 days of home monitoring, a minimum of 3 full days of home monitoring data will be considered adequate (this allows for lost data due to technology malfunction/user error/illness/etc.).
3. Week 8 Assessment Window: A ± 2-week (± 14 days) window around the Week 8 assessment will be considered allowable for data collection, as long as participants have not allowed modafinil treatment to lapse/run out during this time period.
4. Home Monitoring Prior to Week 12: The Week 12 PRO-Diary home monitoring data collection will ideally commence 7 days prior to the final day of modafinil administration. A minimum of 3 days of monitoring during the final week of modafinil administration will be acceptable for completion of this data collection, as no monitoring should take place after modafinil has stopped; monitoring will cease following the last day of modafinil treatment even if an entire 7 days of data has not been collected.
5. Week 12 Assessment Window: The Week 12 survey (REDCap) assessment can be completed up to 2 weeks (-14 days) prior to the Week 12 visit, but if possible should be completed within the final week of modafinil treatment, and no later than final day of modafinil administration.

6. Week 24 Assessment Window: A ± 1-month (± 30 days) window around the Week 24 period will be allowed for collection of follow-up data.

6.7 Treatment Windows

CBT: For participants randomized to receive CBT, treatment will commence as soon after the last day of baseline PRO-Diary monitoring as therapist/participant schedules will allow. Efforts will be made to complete 1 session per week for 8 consecutive weeks (main treatment sessions) followed by 2 approximately every-other-week maintenance sessions (maintenance sessions). However, flexibility in the scheduling of these sessions will allow for, at a minimum, completion of the 8 main treatment sessions within the 12-week treatment period. If needed, scheduling of >1 session/week, but no more than 2 sessions in a 7-day period is allowable to ensure that the full treatment is delivered in the 12-week treatment period. No treatment sessions will be delivered beyond the 12-week treatment period.

Modafinil: For participants randomized to receive modafinil, treatment will commence the day after the last day of baseline PRO-Diary monitoring, and continue for a period of 12 consecutive weeks. For patients receiving combination therapy, Modafinil will start on or before first day of CBT.

6.8 Participant Compensation

Participants will be compensated $300 for full completion of the study. For those who do not complete all study assessments, the compensation schedule is noted on the consent form and is as follows:

Baseline Assessment: Participants will receive $100 for fully completing the baseline REDCap surveys and home monitoring period assessment. For those who do not complete both components of the baseline assessment, participants will receive $25 for completing REDCap survey measures & $75 for completing the home monitoring period assessments (minimum 3 days of data).

Week 8 Assessment: Participants will receive $50 for completing the Week 8 REDCap surveys.

Week 12 Assessment: Participants will receive $100 for fully completing the Week 12 REDCap surveys and home monitoring period assessment. For those who do not complete both components of the Week 12 assessment, participants will receive $25 for completing REDCap survey measures & $75 for completing the home monitoring period assessments (minimum 3 days of data).

Week 24 Assessment: Participant will receive $50 for completing the Week 24 REDCap surveys.

Participants will be compensated for assessments after each completion; thus, they may be remitted up to four separate payments, after completion of each assessment period.

6.9 SCHEDULE OF ACTIVITIES

Study Activity	Baseline (week -1 to -2)	Weeks 1-7**	Week 8	Weeks 9-11	Week 12	Weeks 13-23	Week 24
Demographics	X						
Medical/Surgical History	X		X		X		X
Interview with a Neurologist for assessment of eligibility	X						
Krupp's Fatigue Severity Scale (FSS)	X						
Patient Health Questionnaire-3	X						
Medication review	X		X		X		X
Baseline urine Pregnancy test if applicable	X						
AE/SAE review (all participants)*	X		X		X		X
Randomization	X						
Modafinil dispensing (for Groups 2 and 3)	X		X				
Study Intervention Administration		X	X	X	X		
Treatment adherence			X		X		
Treatment Utilization Patterns (post-intervention)							X
Excess modafinil destruction (if applicable)					X		
Computer-based self-report measures							
Modified Fatigue Impact Scale (MFIS)	X		X		X		X
EDSS self-report	X						
STOP-BANG questionnaire	X						
RLS Index	X						

Epworth Sleepiness Scale	X		X		X		X
Insomnia Severity Index	X						
Sleep Hygiene Index	X		X		X		X
Patient Health Questionnaire-8	X		X		X		X
Generalized Anxiety Disorder-7	X		X		X		X
Brief Pain Inventory	X		X		X		X
Exercise (Godin)	X		X		X		X
PROMIS Self-Efficacy Scale	X		X		X		X
PROMIS Cognitive Function	X		X		X		X
MSQOL54- Quality of Life Subscale	X		X		X		X
NeuroQoL Ability to Participate in Social Roles & Activities	X		X		X		X
Post-Treatment Questionnaire					X		X
Patient Global Impression of Change					X		X
7-day home monitoring (PRO-Diary) measures							
Physical Fatigue Severity (4x/day)	X				X		
Mental Fatigue Severity (4x/day)	X				X		
Physical Fatigue Impact (4x/day)	X				X		
Mental Fatigue Impact (4x/day)	X				X		
Wake up time (1x/day)	X				X		
Bed time (1x/day)	X				X		
Sleep refreshed (1x/day)	X				X		
Rest breaks (1x/day)	X				X		
Cognitive clarity (1x/day)	X				X		
Cognitive speed (1x/day)	X				X		

Pain Severity (1x/day)	X				X		
Daytime physical activity (continuous)	X				X		

* For Modafinil-treated participants in Group 2 and 3, AE/SAE review will be additionally assessed at the following time intervals:
- 2-4 days after starting Modafinil
- 7-10 days after starting Modafinil

**Activities marked Week 1-7 begin after the baseline assessments, which include a 7-day home monitoring period.

7. ASSESSMENTS

7.1.1 Primary Outcome Assessments (see also section 7.1.3)

The Modified Fatigue Impact Scale (MFIS, primary outcome measure)[1,2]: is a patient-reported 21-item validated measure of fatigue impact based on patients' recent personal experience as it relates to physical, cognitive, and psychosocial functioning. The MFIS has been shown to be sensitive to changes secondary to interventions. Scores range from 0-84. Higher scores indicate more fatigue.

7.1.2 Secondary/exploratory outcome assessments, effect modifier measures, screening measures (see also section 7.1.3)

Self-reported Expanded Disability Status Scale (SR-EDSS)[3]: is a validated self-report version of the clinician-administered EDSS; scores on the SR-EDSS correspond highly with clinician-rated EDSS.

STOP-Bang Questionnaire: The STOP-Bang is a validated, 8-item screening instrument that assesses characteristics known to confer risk for OSA, and form the acronym "STOP-BANG" (Snoring, Tiredness, Observed apneas, high blood Pressure, BMI, Age, Neck circumference, Gender).[4] Item scores (1/0) are based on yes/no answers. Scores ≥3 indicate elevated risk for sleep apnea.

Krupp's Fatigue Severity Scale (FSS)[5] – I/E criterion: The FSS is a validated, 9-item instrument that measures the impact of fatigue on multiple outcomes, with a physical focus. Prior studies have shown acceptable internal consistency and stability over time, and sensitivity to change that correlates with the subject's clinical improvement. Many if not most past studies on MS-related fatigue have used the FSS.

Epworth Sleepiness Scale (ESS)[6]: The ESS is an 8-item questionnaire that asks about the likelihood of dozing in variably sedentary situations. This commonly used measure of subjective sleepiness, or sleep propensity, is reliable, internally consistent, and validated against objective polysomnographic measures. A score ≥10 suggests excessive sleepiness.

Insomnia Severity Index (ISI)[7,8]: The Insomnia Severity Index (ISI) is a 7-item questionnaire with 5-point Likert scale responses designed to assess the nature, severity, and impact of insomnia in adults. Scores of 15 or higher reflect moderate clinical insomnia.

Sleep Hygiene Index (SHI)[9]: The Sleep Hygiene Index is a 13-item self-report measure designed to assess the practice of sleep hygiene behaviors. Each item is rated on a five-point scale ranging from 0 (never) to 4 (always). Total scores range from 0 to 52, with a higher score representing poorer sleep hygiene .

Restless Legs Syndrome Diagnostic Index (RLS-DI)[10,11]: is a 10-item questionnaire designed to improve diagnostic decision making in suspected cases of RLS. This instrument incorporates essential diagnostic criteria with additional supportive criteria to rule out false positive cases, which can occur in patients with MS. A score of +11 yields a 93% sensitivity and 96% specificity to diagnose RLS.

The Patient Health Questionnaire –8 (PHQ-8)[12]: assesses frequency of 8 depressive symptoms in the past 2 weeks. It has been validated in MS and provides clinical cut-points ranging from no depression to severe depression (range 0-24).

Patient Health Questionnaire-2[12,13] plus item 9/i from the PHQ-9[14] (PHQ-3) – I/E criterion: assess the frequency of 3 depressive items in the past two weeks. The PHQ-2 has been validated as a depression screen and item 9/i from the PHQ-9 is used to assess for suicidal ideation.

The Brief Pain Inventory (BPI)[15,16]: assesses both pain intensity (4 items) as well as pain interference in multiple life domains (7 items) and has demonstrated good psychometric characteristics, including validity, in MS.

The Generalized Anxiety Disorder – 7 (GAD-7)[12,17]: is a commonly used anxiety measure that assess 7 symptoms of anxiety in the past 2 weeks, and provides clinical cut-points for anxiety severity (scores range 0 – 21).

The Godin Leisure-Time Exercise Questionnaire[18]: is a brief, 4-item measure of the frequency and intensity of exercise during "a typical week" that has been frequently used in MS clinical research and has even been used to validate accelerometer measures of physical activity in MS.

Neuro-QoL Ability to Participate in Social Roles & Activities 8-item Short Form[19,20]: is an 8-item measure of a person's ability to participate in various social roles and activities across a range of social domains (home/family, recreation). Raw scores range from 8-40, with higher scores indicating better ability to participate. T scores, with a Mean=50 and SD=10 can be calculated for comparison to a normative sample of individuals with neurological conditions. This measure has been validated in MS.

Patient Reported Outcomes Measurement Information System (PROMIS) Self-Efficacy for Managing Symptoms Short Form 8a[21,22]: is an 8-item measures developed to assess confidence or self-efficacy for managing symptoms and is meant to be used across clinical conditions. Raw scores range from 8-40 and T-scores have a Mean=50, SD=10; higher scores indicate greater self-efficacy.

Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Abilities Short Form 8a: is an 8-item measure that assesses perceived cognitive function. Raw scores range from 8-40 and T-score have a Mean = 50, SD=10; higher scores indicate greater cognitive functioning. This measure has demonstrated good reliability and validity in MS[23].

Patient Global Impression of Change (PGIC)[24]: is a commonly-used single-item measure that assesses perceived overall change across multiple life domains since beginning treatment. Higher scores indicate greater improvement since treatment was initiated.

Quality of Life Subscale from the Multiple Sclerosis Quality of Life-54 Instrument[25-27]: contains two items that assess perceived general quality of life. The possible range is 0-100 with higher values indicating higher quality of life.

Post-Treatment Questionnaire; contains questions about the patient intent to continue the treatment they received during the 1st 12 weeks (on a clinical basis), their reasons for doing so, and means/barriers to obtaining this treatment. This questionnaire will be administered at 12 and 24 weeks.

Ecological Momentary Assessment (EMA) measures: Eleven EMA items were created (adapted from validated surveys) to assess fatigue, fatigue impact, sleep, pacing, cognitive function, and pain. EMA items are as follows:

1) Physical Fatigue (four times daily):
What is your level of physical (bodily) fatigue right now? on a scale of 0 – 10, where 0 = No Fatigue and 10 = Extremely Severe Fatigue.
2) Mental Fatigue (four times daily):
What is your level of mental (brain) fatigue right now? on a scale of 0 – 10, where 0 = No Fatigue and 10 = Extremely Severe Fatigue.
3) Physical Fatigue Interference (four times daily):
How much is your physical fatigue interfering with what you are doing right now? on a scale of 0 – 10, where 0 = no interference and 10 = totally interfering; not able to do what I want because of fatigue. Slight change in wording for bedtime: How much did your physical fatigue interfere with what you were doing leading up to your bedtime? On a scale of 0 – 10, where 0 = no interference and 10 = totally interfered, was not able to do what I wanted because of fatigue.
4) Mental Fatigue Interference (four times daily):
How much is your mental fatigue interfering with what you are doing right now? on a scale of 0 – 10, where 0 = no interference and 10 = totally interfering; not able to do what I want because of fatigue. Slight change in wording for bedtime: How much did your mental fatigue interfere with what you were doing leading up to your bedtime? On a scale of 0 – 10, where 0 = no interference and 10 = totally interfered, was not able to do what I wanted because of fatigue.
5) Wake Up Question (administered once daily):
What time did you wake up this morning?
6) Go To Bed Question (administered once daily):
What time did you go to bed [last night]?
7) Sleep (administered once daily at wake):
How refreshed did you feel when you woke up this morning? on a scale from 0-10 where 0=Totally Unrefreshed (not at all rested) and 10=Totally Refreshed (restored, revitalized, ready to start the day).
8) Rest Breaks (administered once daily at bedtime)
Today, how often have you taken rest breaks to do your activities? On a scale where 0 = Not at all, 5 = Sometimes, and 10 = Always.
9) Cognitive Clarity (administered once daily at bedtime)
Today, on average, my thinking was: Please rate on a scale of 0-10 where 0 = very clear to 10 = very foggy
10) Cognitive Speed (administered once daily at bedtime)
Today, on average, my thinking was: Please rate on a scale of 0 – 10, where 0 = very fast to 10 = very slow

11) Pain (administered once daily at bedtime) Today, what was your average level of pain? On a scale where 0 = no pain at all and 10 = worst pain imaginable

Covid Impact Survey: The COVID-19 Impact Survey was designed to assess impacts of COVID-19 on participants that could have an effect on study outcomes. It was adapted from the COVID-19 Exposure and Family Impact Survey (CEFIS), developed by The Center for Pediatric Traumatic Stress. Part 1 consists of 22 items that measure the participants' "exposure" to COVID-19 and related events. The Exposure Score is a count of "yes" responses and may range from 0 to 22. Part 2 consists of 13 items that measure the impact of COVID-19. 10 items use a five-point Likert scale rating impact on participant's and family's life; 1 item uses an 11-point distress scale. Higher scores denote more negative impact / higher distress. The Impact Score (sum of items 23-35) may range from 12 to 70. Part 3 is an open-ended question so that participants can expand upon their experiences and add effects of COVID not covered in the other questions.

7.2 Data Collection Technologies

7.2.1 The PRO-Diary

The PRO-Diary is a wrist-worn accelerometer enhanced with a user interface that allows for input of real-time self-reported data. The PRO-Diary will be 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 will be initiated by the participant upon waking (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 audible alarm will alert participants to use the touch screen to log symptom ratings at 2 times between 11am and 7pm. 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.

7.2.2 REDCap

This study will use REDCap, 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 will be used to send the follow-up survey links. Participant emails will be stored in REDCap. The University of Washington study staff will be able to view only email addresses of University of Washington participants, but as the data coordinating center, the University of Michigan study staff will have access to email address for all study participants, including those from University of Washington.

7.2.3 M+Box

Transfer (from UW to UM) of accelerometer/EMA data from the PRO-Diary will be achieved via M+Box, which is Michigan's implementation of the Box.com cloud storage and collaboration service. It 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.

7.2.4 SignNow

This study will use SignNow to request and obtain digital signatures on informed consent document from participants who conduct their baseline visit virtually. SignNow software is an E-Signature service available for use by U-M staff, faculty, researchers, and students associated with all University of Michigan campuses (i.e., Ann Arbor, Dearborn, Flint and Michigan Medicine). SignNow is HIPAA and FDA 21 CFR Part 11 compliant for patient signatures.

7.3 General Medical History

General medical history will be assessed at baseline and in all follow-up visits. Subjects will be queried about any chronic or ongoing health conditions pertinent to MS, fatigue, or potential Modafinil side effects that require treatment (which will be recorded in the CRF). Subjects will also be asked to provide their list of medications and allergies.

7.4 Concomitant Medication Use

Concomitant medications will be assessed at each visit and/or phone contact and recorded in the CRF.

7.5 Adverse Event Assessments

Adverse events that are NOT related to the normal course or chronic symptoms of MS (such as relapses, MRI progression, somatic pain, weakness, numbness, visual disturbances, bladder/bowel symptoms) or events that are expected to occur in the course of daily life or use of disease modifying therapy (injuries, infections, disease modifying therapy infusion reactions, disease modifying therapy injection site reactions, disease modifying therapy-induced lymphopenia) **will be assessed/collected at each visit, scheduled phone call, or unscheduled phone call.**

Participants will be queried about any symptoms they have been experiencing while on the study, with directed questions toward adverse outcomes previously reported with the study treatments (including headache, nausea, nervousness, rhinitis, diarrhea, anxiety, insomnia, dizziness, dyspepsia, worsening depressive symptoms, psychosis, increased suicidality) or suspected allergic reactions: rash, hives, mouth sores, blisters, swelling of your face, eyes, lips, tongue, or throat, trouble swallowing or breathing, fever, shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

8. ADVERSE EVENT REPORTING

Multiple Sclerosis is a disease with many disease-related symptoms and complications, and there are many common mild side effects associated with disease modifying therapy use. Due to the patient population and the nature of the disease, as well as the lack of experimental interventions in this study (only standard of care procedures and treatments will be used) we would like to implement the following AE/SAE collection/reporting guidelines:

SAE events that meet all 3 of the following criteria will be collected and submitted to the IRB:

- Serious;
- Related; and
- Unexpected

SAEs that are unrelated, regardless of expectedness, will not be reported to the IRB.

In addition, the following AEs will be collected and submitted to the IRB:

- Any related and unexpected AE that results in a change to research or participant's treatment plan

The medical monitor (see section 10.2) will also receive reports of all AEs collected in section 7.5, and SAEs regardless of expectedness or relatedness.

8.1 AE/SAE relatedness:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

8.2. Serious Adverse Events (SAE) Definition: An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience

c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.

Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

8.3 AE/SAE Expectedness:
Expected adverse events are those adverse events that are listed in the protocol, the Investigator's Brochure (current edition) or in the study informed consent document.

Unexpected adverse events are those that:

a. are not described in the Investigator's Brochure, approved label, or the clinical protocol as far as the study drug is concerned.
b. are not anticipated in the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

Unanticipated problem: Per FDA Procedural Guidance for Clinical Investigators, Sponsors, and IRBs (January 2009), a serious problem that has implications for the conduct of the study (requiring a significant and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent or investigator's brochure).

Unanticipated problem Reporting: Per 21 CFR 312.66, 312.53 (c)(1)(vii), and 56.108(b)(1), should an Unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involving risks to human subjects or others to IRBMED and FDA according to the reporting requirements and guidelines.

8.4 AE/SAE severity: *The severity or grade of an adverse event may be measured using the following definitions:*

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

9.0 DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

Estimates are derived from recent data from the study team, and published interventional studies of modafinil and CBT monotherapy. The primary sample size determinant for this study is Aim 1.

For Aim 1, we have chosen the Modified Fatigue Impact Score (MFIS) as 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. The primary outcome measure will be 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 (see power curve); this difference is similar to group differences found in previous fatigue trials.

For Aim 2 analyses, using fatigue outcomes as the dependent variables (in separate models) a multiple linear regression power analysis was performed assuming a full model consisting of up to 11 possible predictor variables: treatment group, presence of sleep disturbance (yes/no), depression severity (PHQ-9 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, we will have 85% power to detect an R-square difference of 0.04 for the interaction term 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.

9.2 Analysis of Study Aims:

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 (HTE analyses). 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”).

9.3 Analysis of Exploratory Aims:

Additional analyses modeled as in 9.2 above will also 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.

Additional analyses modeled as in 9.2 above will also evaluate 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 12-24 weeks, following the 12-week intervention interval.

Analyses modeled as in 9.2 will also be used to evaluate treatment effects on other outcomes at 12 and 24 weeks. 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 in models similar to the approach described in 9.2.

If potential mediators of the treatment effects, such as self-efficacy for managing symptoms, sleep, depressed mood, and anxiety, 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.

10. MONITORING

10.1 Data Safety Monitoring Plan

The Clinical Trial Monitor from the Michigan Institute of Clinical Health Research (MICHR) will set up a monitoring plan to include scheduled and as needed in person and remote monitoring visits to confirm the accuracy of study data, review study documents (including informed consents), and assess compliance with human subjects research.

10.2 Independent Medical Monitor

This study also has an assigned medical monitor who is not part of the study team (Brandon Moss, MD). The primary responsibilities of the Medical Monitor include:

1. Provide feedback for protocol changes, if needed
2. Review/provide written feedback/sign off on captured AEs and withdrawals annually (in aggregate, to coincide with annual IRB continuing review)
3. Review/provide verbal feedback/sign off SAEs/unanticipated problems as they arise, depending on relatedness of the intervention
4. Assist with decisions about treatment withdrawal or dose reduction, on a case by case basis as they arise, for AEs thought to be probably related or definitely related to one of the interventions, regardless of expectedness.

10.3 Monitoring Plan and Information

To assure adequate protection of the rights of human subjects, per 21 CFR 312.50 and 312.53, the study will be 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.

A qualified trial monitor will be selected, per 21 CFR 312.53(d) to monitor this multi-site trial in accordance with the protocol and all applicable regulatory requirements. A monitoring plan will be established to ensure the quality and integrity of the data through pre-investigation, periodic site visits (both sites), review of adverse events/subject records, etc. The Michigan Institute for Clinical and Health Research (MICHR) will assist with the selection and support of the monitor assigned for this proposed clinical investigation and prepare the monitoring plan.

11. DATA HANDLING AND RECORD KEEPING

11.1 CRFs / Electronic Data Record

CRFs, in paper or electronic format, will be utilized and maintained by the study staff. Entries made in the CRF must be verifiable against source documents, unless the CRF is considered to be the source document.

11.2 Record Retention

Per 21 CRF §312.62, study records will be retained for a minimum of 7 years after the investigation is discontinued.

12. ETHICS

12.1 Institutional Review Board

Prior to study commencement, the study will be reviewed and approved by the Institutional Review Board (IRBMED, University of Michigan, Ann Arbor, MI).

12.2 Subject Information and Consent

A study team member will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent will be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and will be submitted for IRB approval.

13. STUDY DISCONTINUATION CRITERIA

Treatment Stopping Rules for Safety Reasons

1. Any SAE, as defined in section 8.2.

2. Psychosis, severe/uncontrolled depression, or increased suicidality. Participant behavior or comments that suggest imminent threat of suicide will prompt immediate 911 activation. Behavior or comments that suggest suicide ideation with plan but no immediate threat will prompt psychiatric ER referral

3. Participants who demonstrate physical, emotional, or behavioral signs that are thought to be probably related or definitely related to one of the interventions, and in whom dose adjustments have failed* or are not an option

Modafinil Specific Stopping Rules for Safety reasons

1. Pregnancy.

2. Suspected allergic reactions: rash, hives, mouth sores, blisters, swelling of your face, eyes, lips, tongue, or throat, trouble swallowing or breathing, fever, shortness of breath, swelling of the legs, yellowing of the skin or whites of the eyes, or dark urine.

3. Participants who decide to start another fatigue treatment medication (stimulant or wake-promoting agent) 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)amantadine, methylphenidate, or amphetamine during the study.

* 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 SAE criteria, will be required to stop modafinil at the dose which was associated with the symptoms, but upon improvement of symptoms, may be allowed to restart the medication at ½ 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.

Off-Study Criteria
For 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.

Discontinuation of a Subject
In the event a patient drops out of the study or is lost to followup, 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.

14. ENGAGEMENT

All patient stakeholders and study team members will participate in regular in-person or webinar meetings. At these meetings, aspects of the study will be reviewed, including study protocol and progress, interim regulatory issues, patient recruitment/enrollment/retention reports, operational issues, adverse events, and treatment adherence. Stakeholders and study team will mutually decide if strategic changes are required, and if so, will require stakeholder approval.

Stakeholders will:

- Participate in study monitoring. If milestones are not met, or are not likely to be met based on current methods, stakeholder feedback will be solicited to enhance delivery of milestones.
- Assist with distribution of recruitment materials.
- Assist with solicitation of clinic patients.
- Participate in development of a pre-screening procedure so that all potentially-eligible patients are identified in a standardized fashion.
- Be involved in authoring and reviewing dissemination materials.

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