Protocol Title: Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS)

NCT03185065

Date: October 24, 2018

List of protocol modifications

Date	Modification	Rationale
7.12.2017	• Added to the inclusion criteria: - Screening MFIS score cutoff was reduced from 38 to 33 - The requirement for fatigue medication washout was decreased from one month to two weeks	Suggested by the study advisory committee
	• Added to the exclusion criteria: - Exception of marijuana and other cannabinoids	Suggested by the study advisory committee
	• To help participants choose the medication that was most effective for them, we added to the protocol that "the pharmacist the study manager will unblind the participants after they finish all study procedures or when they stop participating in the trial for any reason."	Requested by the IRB
	• Added: "If the participants tolerate the study medications without developing any side effects, they will be allowed to titrate the medication according to the above schedule, even if they do not receive such instructions from the study nurse. Those participants who develop new or worsening symptoms, are not allowed to titrate the medication before receiving such instructions from the study nurse.	Suggested by the study advisory committee
	• Added:" If physical examination and/or EDSS is performed by one of the neurologists in the participating centers (JHU or UCSF) during a clinical encounter in 30 days prior to the screening visit and the results were available for review at the time of screening, there is no need to repeat them and we will use those data during the screening. The screening labs will be collected if the screening visit MFIS score is >33. If the required labs were done in 30 days prior to screening and the results were available for review at the time of screening, there is no need to repeat the labs (except the urine pregnancy test)."	Suggested by the study advisory committee
	• Removed from study procedures: "Positive and Negative Affect Schedule"	Suggested by the study advisory committee
	• Added the question to the study procedures: "Going forward, would you choose this medication as your fatigue treatment?"	Suggested by the study advisory committee
	• Reduced the frequency of DSMB conference calls from quarterly to every six months	Suggested by the study advisory committee
8.17.2017	• Changed one of Exclusion criteria:	Requested by the DSMB

	- Changed the "serum creatinine >2.0 at screening" to "GFR (glomerular filtration rate) < 50"	
	• To increase flexibility, the washout period between study period changed from "a two-week washout period" to "a minimum of two weeks of washout"	Suggested by the study advisory committee
	• Added:" For the first treatment period, if the participant's eligibility is confirmed while s/he is still at the screening visit, the study team can randomize the participant and dispense the first period medication to the participant."	Suggested by the study advisory committee
	• We clarified the color of capsules: changed light-colored to "orange/red" and dark-colored to "blue".	Clarification of the protocol
	• Added a window of ±3 days to the scheduled phone calls to participants.	Suggested by the study advisory committee
	• Changed: "Participants will start taking the study medication of the first period of their assigned sequence within 60 days <u>(instead of one month)</u> after the screening visit.	Suggested by the study advisory committee
3/15/2018	• Added the following exclusion criteria: - History of long QT syndrome, atrial fibrillation or tachyarrythmias (other than sinus tachycardia) - History of ischemic or hemorrhagic stroke - History of glaucoma - History of Tourette syndrome	Suggested by the PI and the study advisory committee
	• For contacting participants during the trial, we added the options of email and text messages and reduced the number of patient contacts to five.	Suggested by the study advisory committee
	• We added the following statement regarding participants dropouts:" If a participant decides to stop the study medication or because of development of adverse events, is instructed by the study team to stop the study medication, the outcome measures of that particular period will be performed during the 5th week of that medication period (i.e. at the scheduled time frame). If the participant is continuing the study and is willing to start the study medication of the next period, as long as they have been off the study medication for at least two weeks and they have answered the outcome questionnaires on week 5, the medication period can be started immediately. If a participant decides to drop out of the study, stop the study medication and start a medication outside of the study,	To clarify the study procedures, Suggested by the study advisory committee

	the outcome questionnaires should be administered while the patient is still on the study medication or before they start a medication outside of the study." • We added the following statement:" If physical examination and/or EDSS is performed by one of the neurologists in the participating centers (JHU or UCSF) during a clinical encounter in three months prior to the screening visit and the results were available for review at the time of screening, there is no need to repeat them."	Suggested by the study advisory committee
10.24.2018	• In the original protocol, we had mentioned that 50% of participants will be recruited at each center. To improve the recruitment, we changed the process:" The enrollment will be competitive: one center may recruit more participants compared to the other center."	Suggested by the PIs and discussed with the PCORI staff

Contents

Synopsis:

Protocol title: Treatment of fatigue with methylphenidate, modafinil and amantadine in multiple sclerosis (TRIUMPHANT-MS)

Indication: Fatigue in multiple sclerosis (MS)

Objectives

To compare the efficacy of commonly used fatigue medications in patients with multiple sclerosis.

Trial design: Randomized, placebo-controlled, crossover, 4-sequence, 4-period, double-blind (participants and investigators), multicenter trial of 3 commonly used medications for treatment of MS-related fatigue (amantadine, modafinil, methylphenidate) versus placebo in fatigued subjects with MS defined by McDonald Criteria.

Number of patients: 136

Target population: Adult patients with MS and fatigue.

Inclusion criteria:

- Age 18 years and older.

- Females of childbearing age must have a negative urine pregnancy test at baseline and use an effective method of contraception during the study.

- Diagnosis of MS (according to the 2010 McDonald criteria).

- Expanded Disability Status Scale (EDSS) score at the time of screening 0.0-7.0.

- Fatigue reportedly present and screening Modified Fatigue Impact Scale (MFIS) score more than 33.

- At least a two-week washout for any fatigue-related drug, including study medications.

Exclusion criteria:

- Neurodegenerative disorders other than relapsing or progressive MS.

- Breastfeeding or pregnant.

- History of coronary artery disease or congestive heart failure.

- Uncontrolled hypertension at screening (history of high blood pressure and screening systolic blood pressure >160 or diastolic blood pressure>100).

- GFR (glomerular filtration rate) < 50.

- Abnormal liver function at screening (AST or ALT more than twice the upper limit of normal).

- Terminal medical conditions.

- Currently treated for active malignancy.

- Planned surgery or move within 8 months of screening.

- Alcohol or substance abuse in the past year (except marijuana or other cannabinoids).

- A history of intolerance or allergic or anaphylactic reaction to amantadine, modafinil, methylphenidate or any component of the preparation.

- Clinically unstable medical or psychiatric disorders that require acute treatment as determined by the PI.

- Concurrent use of monoamine oxidase inhibitors-B.

- Hypersensitivity/idiosyncrasy to sympathomimetic amines

- Inability to communicate or answer the questionnaires in English or Spanish.

- Severe untreated anemia (blood hemoglobin <9gr/dl)

- History of untreated hypothyroidism

- History of untreated sleep apnea

- History of long QT syndrome, atrial fibrillation or tachyarrythmias (other than sinus tachycardia)

- History of ischemic or hemorrhagic stroke

- History of glaucoma

- History of Tourette syndrome

Study duration: Study participation period includes screening period and treatment period.

- Screening period duration is one months.

- Treatment period is 6 weeks for each study drug.

Investigational products: Participants will receive amantadine, modafinil, methylphenidate and placebo in a randomly assigned sequence (Figure 1 on page 13). Each medication will be titrated over four weeks to the participants' highest tolerated dose or the pre-defined highest dose. The dosing and titration schedule of the study medications are depicted in Figure 2 on page 13:

Assessments:

Efficacy: Questionnaires- Modified fatigue impact scale (MFIS), NeuroQOL fatigue item bank

Safety: Safety blood tests, urine pregnancy test, adverse event collection, concomitant medication review

The primary efficacy outcome is the MFIS score at the end of each treatment period. The secondary efficacy outcome is the average Neuro-QoL fatigue item bank score at the end of each treatment period.

Study locations: This study will be conducted at the University of California San Francisco (UCSF) and Johns Hopkins University (JHU).

Sample size and statistical analysis

With an intraclass correlation coefficient (ICC) of 0.7, power of 90% and type one error of 0.05 (Bonferroni corrected for 6 pairwise comparisons), we will need 91 patients to detect at least a 10-point difference in MFIS between the placebo and medication groups. Assuming 20% dropout within each treatment period, the total sample size for the proposed trial will be 136 subjects.

We will use a linear mixed-effect regression model for the primary outcome measure of the study (MFIS total score) while taking maximal tolerated or target dose in each treatment period as the independent variable, and the study medication, treatment sequences, treatment periods and study sites as the fixed effects with the subjects as the random effect. If this test is significant at the 0.05 level, we will make pairwise comparisons between study treatments using estimated contrast at 0.05 level. The secondary efficacy outcome will be analyzed using a similar mixed-effect model.

The safety outcome will be analyzed by including all subjects who have received at least one dose of study medication. Participants will be analyzed according to the actual treatment received. The assessment of safety will be based on the frequency of adverse events. Tolerability of medications will be reported as the range, median and average highest tolerated dose for each medication.

Data Collection Method

We will use Redcap (http://project-redcap.org/), a secure web application for building online databases, as the trial data management software. It is housed at UCSF. Most of the trial data, including screening and baseline values of MFIS and questionnaires answered in each study period will be directly captured via REDCap forms by the participants. If a participant cannot enter data online, (s)he will complete a paper form and mail it to the study coordinator who will perform data entry. Alternatively, the study coordinator will call the subject who will answer questions on the phone, and data will be entered at that time by the study coordinator.

1. Introduction

1.1 Background

Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) which is the most common cause of non-traumatic disability in

young adults (Frohman et al., 2006). MS usually presents with focal neurological deficit affecting motor function, sensation, balance, vision and bladder and bowel function. Additional symptoms such as fatigue can also contribute greatly to disability. Fatigue, defined by a subjective lack of physical or mental energy perceived by the individual with usual activities, is in fact the most common and one of the most disabling MS symptoms as it affects at least 75 percent of patients at some point (Krupp, 2006, Janardhan and Bakshi, 2002; Lerdal et al., 2007). Although fatigue is commonly seen in many chronic conditions (particularly inflammatory diseases and cancers), it may have distinct characteristics in MS. Fatigue limits patients' daily activities and communications (Blaney and Lowe-Strong, 2009) and results in loss of work hours and employment, with substantial socioeconomic consequences (Smith and Arnett, 2005). Some have suggested that fatigue might impact patients' quality of life as much as ambulatory issues (Foley and Brandes, 2009). However, research to elucidate its pathophysiology has not been very fruitful (Induruwa et al., 2012). The multiple factors that can contribute to fatigue in MS further complicates the picture. Primary fatigue is thought to be mainly due to immunological derangement and CNS damage; however, several other conditions that are commonly seen in patients with MS, such as sleep problems related to legs spasms, urinary changes, and depression can add to the burden of fatigue and can be difficult to distinguish from primary fatigue (Braley and Chervin, 2010).

Despite its prevalence and social impact, fatigue treatments have been inconsistently studied (Toosy et al., 2014) in part due to the above-mentioned complexity of quantification as well as difficulty to discriminate primary fatigue from other contributing factors. Yet to be defined biological processes and lack of clear treatment targets have also hampered the development of drugs for fatigue. As a result, there are no medications approved by the Food and Drug Administration (FDA) for the treatment of MS fatigue. Although several agents have been tested for fatigue, methodological limitations in the design, execution and reporting of those trials have not allowed meta-analyses or systematic reviews to conclude about efficacy. Instead systematic reviews have recommended performing rigorously designed trials to confirm drug effect (Pucci et al., 2007; Tejani et al., 2012). Moreover, the rare head-to-head clinical trials comparing different medications have been small and provided inconsistent results (Ledinek et al., 2013; Shaygannejad et al., 2012; Tomassini et al., 2004). The most commonly used medications for the treatment of MS fatigue in clinical practice are amantadine, modafinil and methylphenidate.

1.1.1. Amantadine

Amantadine is an FDA-approved medication for the prophylaxis of influenza and symptomatic treatment of Parkinson's disease, and is probably the most widely studied medication for MS fatigue. Amantadine has anticholinergic properties, changes dopamine release in the striatum and blocks N-methyl D-aspartate (NMDA) glutamate receptor (Yacoubian and Standaert, 2009). It is not clear which pharmacologic effect of amantadine may be responsible for its possible anti-fatigue properties in MS. Despite multiple randomized controlled trials of amantadine for MS fatigue (Geisler et al., 1996; Krupp et al., 1995; Ledinek et al., 2013; Rosenberg and Appenzeller, 1988; Stein et al., 1995; Tomassini et al., 2004), methodological issues and conflicting results have

prevented any final conclusion on effectiveness. A Cochrane systematic review concluded that the efficacy of amantadine in treating MS fatigue is poorly documented and emphasized the need for good quality randomized controlled trials (Pucci et al., 2007).

1.1.2. Modafinil

Modafinil is a non-amphetamine wake-promoting agent that is FDA-approved for treatment of narcolepsy, obstructive sleep apnea and shift work sleep disorder (Lange et al., 2009). Its mechanism of action is not fully elucidated; however, it is believed to increase cortical activity in the frontal lobes (Kumar, 2008). Three trials in MS fatigue produced inconsistent results. While two well-designed randomized trials reported no effects (Ledinek et al., 2013; Stankoff et al., 2005), another non-randomized trial reported clear benefits at the lower dose (Lange et al., 2009). A systematic review of modafinil as a treatment of fatigue in MS and several other neurological disorders concluded that clinical trials have provided inconsistent results (Sheng et al., 2013).

1.1.3. Psychostimulants

Psychostimulants have also been used for treatment of fatigue in various chronic conditions. The only randomized controlled trial of psychostimulants in MS fatigue was performed using pemoline, a medication used for treatment of attention deficit hyperactivity disorder (ADHD) (Weinshenker et al., 1992). This study concluded that pemoline may be an effective short-term treatment for MS fatigue, but was poorly tolerated. This medication is currently not available in the US. The results of trials using different doses of pemoline were also inconsistent, leaving open the question of the benefit of stimulants for MS fatigue (Krupp et al., 1995; Weinshenker et al., 1992). Methylphenidate, an amphetamine-like psychostimulant approved for the treatment of ADHD, has been studied in several randomized controlled trials of fatigue in conditions other than MS (Breitbart et al., 2001; Cueva et al., 2012; Escalante et al., 2014; Kerr et al., 2012). Interestingly, the results of those trials have also been conflicting. Despite lack of evidence, methylphenidate is commonly used for the treatment of MS fatigue (Krupp and Christodoulou, 2001). While lisdexamfetamine, another amphetamine-like stimulant, improved processing speed and memory in cognitively impaired MS patients, it did not affect fatigue in a phase II randomized controlled trial (Morrow et al., 2013). Conflicting trial results were also reported about anti-fatigue effects of dextroamphetamine in cancer and human immunodeficiency virus infection-related fatigue (Auret et al., 2009; Wagner and Rabkin, 2000).

1.2. Comparative effectiveness studies of fatigue medications

As reviewed above, despite the severity and pervasiveness of fatigue in MS, there is no high quality evidence supporting the use of any of the three commonly prescribed medications for the treatment of MS-related fatigue (amantadine, modafinil and methylphenidate) (RQ-1). There has been no head-to-head comparison of amantadine, modafinil and amphetamine-like psychostimulant in MS patients. A small multi-arm trial that included amantadine, modafinil and placebo, reported superiority of amantadine to placebo and no difference in the effect of

modafinil to placebo, but didn't compare amantadine versus modafinil (Ledinek et al., 2013). There is a need to confirm efficacy and tolerability of drugs broadly used to treat MS fatigue.

1.3. Rational for performing this clinical trial

Disease-modifying treatments for MS reduce the incidence of relapses and inflammatory activity on magnetic resonance imaging (MRI), and may be associated with reduced long-term disability. In the era of broad use of disease-modifying treatments and reduced disease activity, treatment of residual symptoms in patients with MS has become increasingly important. Effective treatment of fatigue could potentially improve substantially the quality of life of patients with MS and their caregivers.

As described above, some of the commonly used medications to treat MS-related fatigue have not been tested in randomized controlled trials (e.g. methylphenidate), trial results have been conflicting (e.g. modafinil) or trial design has been inadequate (e.g. amantadine). Hence, evidence-based recommendations cannot not be made to support the use of any agents for MS fatigue.

The proposed randomized double-blind controlled trial will provide high quality evidence for or against the use of study medications: 1) we will have adequate power to show superiority of any tested agent over placebo or comparator, 2) we will have adequate allocation concealment and randomization, so blinding is adequate, 3) we will use a well-studied, valid and reliable instrument to measure MS-related fatigue, 4) and we will assess the clinical relevance of any treatment effect by evaluating quality of life changes during the study.

The medications we propose to test in this study are FDA-approved for use in other conditions and have been used by patients with MS and other neurological condition for many years; thus, their side effect profile is well known. By providing evidence for superiority of one of these agents over the others (or lack thereof), the results of the proposed trial will be readily translated to clinical care. Evidence-based treatment of this very common and disabling MS symptom will improve patient outcomes and reduce the incidence of unwarranted adverse effects of less (or non-) efficacious medications.

2. Study objectives

2.1. Primary objective

To determine within-subject effect of treatment with amantadine versus modafinil versus methylphenidate versus placebo on MS fatigue in a randomized double-blind placebo-controlled crossover trial. We hypothesize that use of amantadine, modafinil or methylphenidate, as compared to placebo, in MS, will be associated with improvement of fatigue scores over 6 weeks of treatment.

2.2. Secondary objectives

- To determine within-subject effect of treatment with amantadine versus modafinil versus methylphenidate versus placebo on fatigue-related quality of life in a randomized double-

blind placebo-controlled crossover trial. We hypothesize that use of amantadine, modafinil or methylphenidate, as compared to placebo, will be associated with improvement of quality of life scores over 6 weeks of treatment.

- To determine the safety and tolerability of treatment with amantadine versus modafinil versus methylphenidate versus placebo in MS fatigue.

3. Investigational plan

3.1. Study design

This is a randomized, placebo-controlled, crossover, 4-sequence, 4-period, double-blind (participants and investigators), multicenter trial of 3 commonly used medications for treatment of MS-related fatigue (amantadine, modafinil, methylphenidate) versus placebo in fatigued subjects with MS defined by McDonald Criteria.

Using a balanced Latin-square crossover design, subjects will be allocated, in a double-blind, randomized fashion, to one of the four treatment sequences (Figure 1): 1) amantadine, placebo, modafinil, methylphenidate; 2) placebo, methylphenidate, amantadine, modafinil; 3) modafinil, amantadine, methylphenidate, placebo; and 4) methylphenidate, modafinil, placebo and amantadine. Each medication will be titrated over four weeks to the participants' highest tolerated dose or the pre-defined highest dose. The dosing and titration schedule of the study medications are depicted in Figure 2. Each treatment period will be 6 weeks and there will be a minimum of a 2-week washout period between each treatment period. At the beginning of the trial, a biostatistician at UCSF will prepare a concealed allocation schedule, randomly assigning the four sequences, in blocks of 4, to a consecutive series of numbers and at the time of enrollment, each participant will be assigned the next consecutive number (and hence the sequence of study medications).

The primary endpoint of the study will be fatigue severity as measured by the MFIS score, between 28th and 35th day of each treatment period (while the patient is taking the maximal tolerated or target dose). The MFIS is a validated patient-reported outcome. The questionnaire will be administered remotely (through internet, phone or mailed forms) and the participants can answer the questions in few minutes while at home or at their work place. The questionnaire has been validated in English and Spanish.

Figure 1- Study sequences.

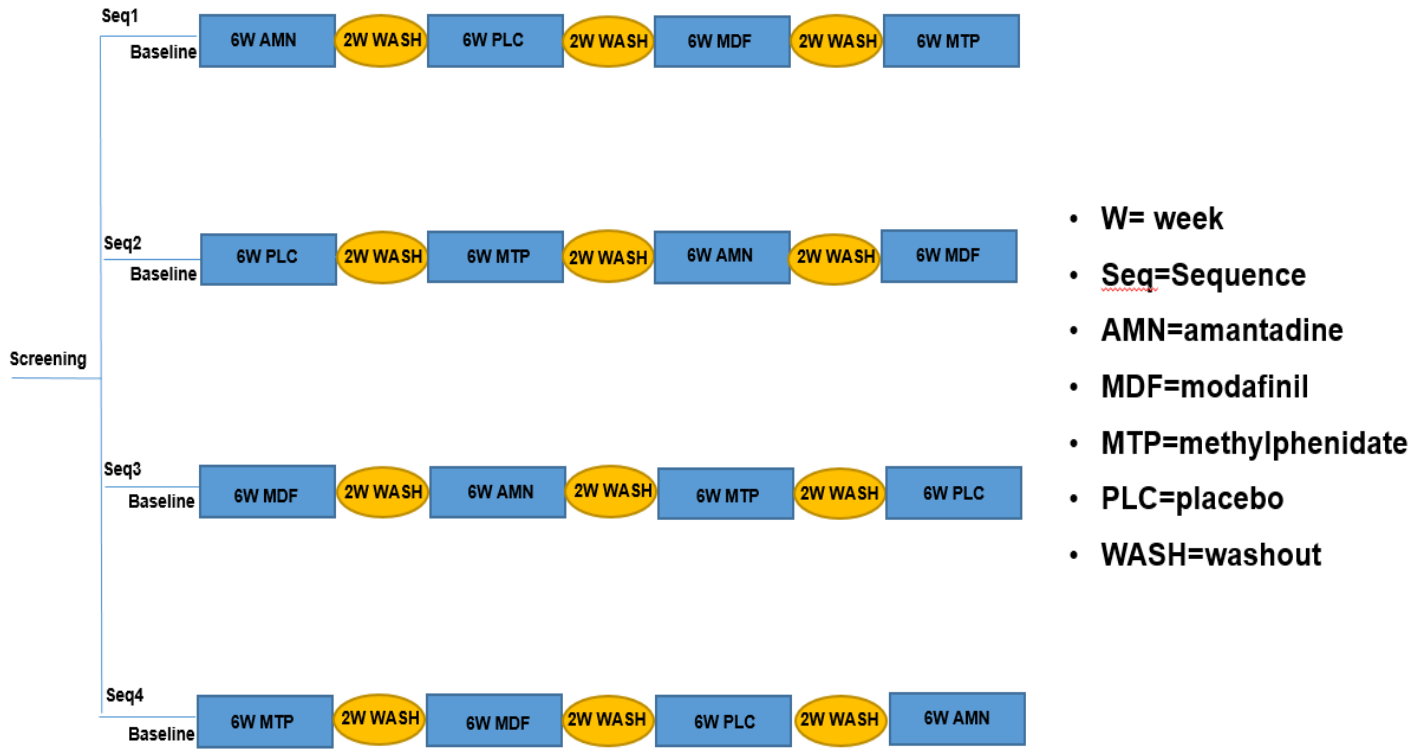
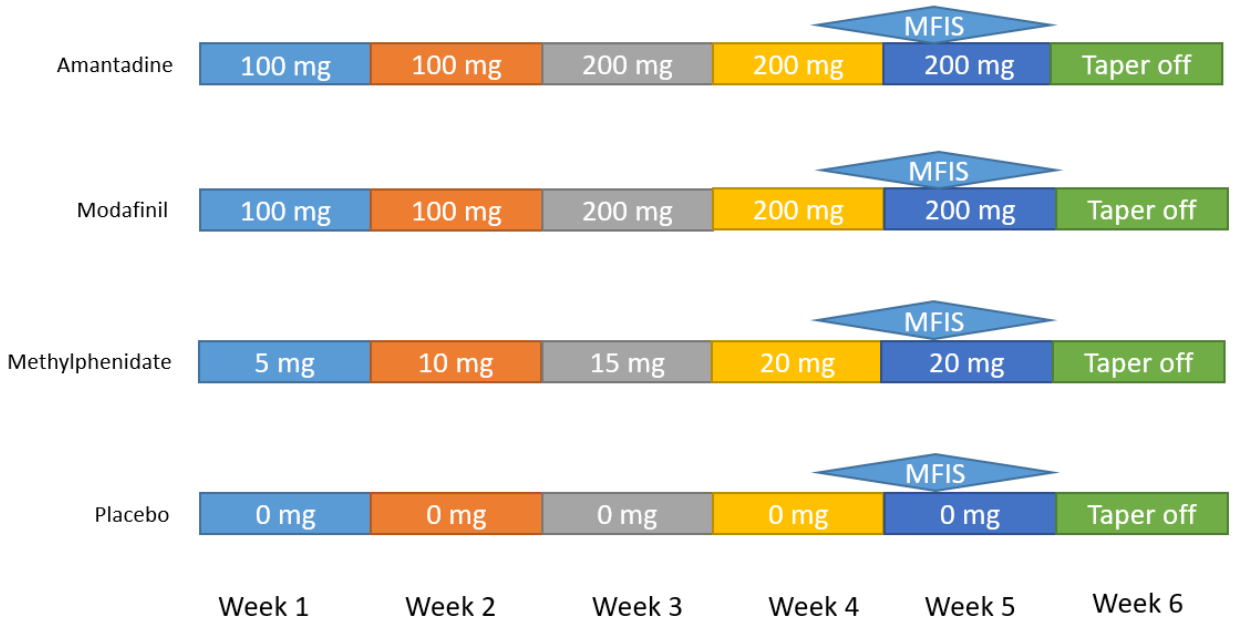


Figure 2- Medication titration schedule.



3.2. Rationale of study design

Performing a pragmatic trial with parallel-group design requires a very large sample size. Our proposal leverages the fact that MS-related fatigue is a chronic condition and symptomatic treatments used in clinic have a short half-life. A crossover design (rather than a parallel-group design) is the best design option that includes several advantages: 1) it will maximize efficiency by using each subject as his or her own control, therefore decreasing sample size and associated costs, and maximizing robustness (i.e. less variability of measurements with within-subject versus between-subjects analyses), and 2) it will likely promote recruitment as all participants will receive all study medications at some point during the study. The short half-life of study medications will allow implementing a minimum of a two-week washout period that will guarantee the absence of a carryover effect that could bias the results of the study.

We will enroll a broad range of subjects with MS including relapsing and progressive forms, across a broad range of disability, and with or without concomitant depression or other comorbidities. As such, the results of the proposed trial will be highly generalizable to MS patients in general. To minimize the chance of harming some participants, we will exclude a small subset of patients who are at high risk of developing complications while receiving study medications, such as patients with uncontrolled hypertension or history of coronary artery disease.

Unlike efficacy or exploratory trials in which all subjects receive a fixed dose of study medication, the participants in our trial will receive the highest tolerated dose of study medications (as opposed to a fixed target dose). Because fatigue fluctuates with the time of the day (Feys et al., 2012), and study drugs have a relatively short half-life, we will assess fatigue severity (primary endpoint) in all participants at a specific time of the day (between 2-5 pm) to maximize consistency and minimize measurement error and variability.

No in-person visits will be scheduled to collect the outcomes of the study after screening. Instead, the outcomes will be collected at participants' home or work place through the web, phone or printed questionnaires. Primary and secondary trial outcomes for the proposed study are patient-reported, validated fatigue severity and fatigue-related quality of life measures that do not rely on central adjudication and can be used to assess fatigue under usual conditions.

There will be no measurements of participant compliance in our study and analysis of primary and secondary outcomes will include all randomized patients regardless of their compliance.

We took into account all the above considerations to design a clinical trial that is closer to the pragmatic end of the pragmatic-explanatory continuum, while maintaining the internal validity of the study and high power to detect a clinically significant change in the severity of fatigue and protect participants' safety and well-being.

3.3. Rationale of dose/regimen and duration of treatment

As a pragmatic trial, comparing the effectiveness of various anti-fatigue medications, the dose of medications is chosen based on the most commonly used regimens by MS neurologist and

previous clinical trial data (if available). For example, although methylphenidate is prescribed in doses over 20 mg/day for treatment of various conditions, it is rare for practicing neurologists to prescribe doses higher than 20 mg/day for treatment of MS-related fatigue.

The effective and tolerated dose of these medications varies among individuals. The titration regimen implemented in this study is trying to assess the efficacy while the participants receive the highest tolerated dose. This regimen will probably improve the medication compliance and provide more realistic information regarding the effectiveness of different medications in improving fatigue in MS.

The duration of each treatment period (six weeks) was chosen based on the assumption that the anti-fatigue effects of these medications is not delayed and the full efficacy of these medications would be apparent after a few days of receiving the highest tolerated dose. Six weeks of treatment period would allow us to safely titrate the medications, measure the trial outcomes while the participants receive the highest tolerated dose, and safely taper off the medications at the end of the treatment period, reducing the possibility of withdrawal symptoms.

We have considered a minimum of a two-week washout period between each treatment period, reducing the possibility of cross-contamination and carryover effects. The duration of the washout period was conservatively based on the half-life of the study medications.

4. Population

Adult patients (men and women aged 18 years and older) diagnosed with relapsing-remitting or progressive MS and reporting fatigue seen at 2 major MS centers in the US (University of California San Francisco (UCSF), and Johns Hopkins University (JHU)). Participants will have diverse racial and ethnic backgrounds, socioeconomic status, MS subtypes and disability. We are planning to screen 177 patients in order to enroll 136 patients in the study. The enrollment will be competitive: one center may recruit more participants compared to the other center, but the total number of enrolled participants will be 136. The study eligibility criteria were chosen to maximize generalizability of the results, while taking into account safety and well-being of the participants.

4.1. Inclusion criteria:

- Age 18 years and older.
- Females of childbearing age (potential) must have a negative urine pregnancy test at screening and use an effective method of contraception during the study.
- Diagnosis of MS (according to the 2010 McDonald criteria).
- Expanded Disability Status Scale (EDSS) score at the time of screening 0.0-7.0.
- Fatigue reportedly present and screening Modified Fatigue Impact Scale (MFIS) score more than 33.
- At least a two-week washout for any fatigue-related drug, including study medications.

4.2. Exclusion criteria:

- Neurodegenerative disorders other than relapsing and progressive MS.
- Breastfeeding or pregnant.
- History of coronary artery disease or congestive heart failure.
- Uncontrolled hypertension at screening (history of high blood pressure and screening systolic blood pressure >160 or diastolic blood pressure>100).
- GFR (glomerular filtration rate) < 50 at screening.
- Abnormal liver function at screening (AST or ALT more than twice the upper limit of normal).
- Terminal medical conditions.
- Currently treated for active malignancy.
- Planned surgery or move within 8 months of screening.
- Alcohol or substance abuse in the past year (except marijuana or other cannabinoids).
- A history of intolerance or allergic or anaphylactic reaction to amantadine, modafinil, methylphenidate or any component of the preparation.
- Clinically unstable medical or psychiatric disorders that require acute treatment or as determined by the PI.
- Concurrent use of monoamine oxidase inhibitors-B.
- Hypersensitivity/idiosyncrasy to sympathomimetic amines
- Inability to communicate or answer the questionnaires in English or Spanish.
- Severe untreated anemia (blood hemoglobin <9gr/dl)
- History of untreated hypothyroidism
- History of untreated sleep apnea
- History of long QT syndrome, atrial fibrillation or tachyarrythmias (other than sinus tachycardia)
- History of ischemic or hemorrhagic stroke
- History of glaucoma
- History of Tourette syndrome

4.3. Pre-specified participant subgroups

- Relapsing-remitting versus progressive subjects.
- Subjects who are not on disease-modifying treatments at the time of enrollment versus those who are.
- Subjects with depression versus those without depression.
- Subjects with mild degrees of disability (EDSS<3.0) versus those with more severe disability (EDSS>=3.0).

5. Treatment

5.1. Investigational treatments

As explained in the background section, amantadine, modafinil and psychostimulants are the most commonly used and studied medications for treatment of fatigue in MS. Although they have been studied and used clinically for many years, their efficacy is still unclear and there is no consensus among experts regarding their clinical utility. Here, we briefly review the medications that we have selected for the proposed study to assess their effectiveness in treatment of MS-related fatigue:

5.1.1. Amantadine: Amantadine is FDA-approved for the prophylaxis of influenza and symptomatic treatment of Parkinson's disease. It was the first medication tried for MS-related fatigue (Hayden, 1996) and is probably the most widely studied medication for this indication. Amantadine has anticholinergic properties, changes dopamine release in the striatum and blocks N-methyl D-aspartate (NMDA) glutamate receptor. (Yacoubian and Standaert, 2009) It is not clear which pharmacologic effect may be responsible for its possible anti-fatigue properties in MS. Despite multiple randomized controlled trials of amantadine for MS fatigue, (Geisler et al., 1996; Krupp et al., 1995; Ledinek et al., 2013; Rosenberg and Appenzeller, 1988; Stein et al., 1995; Tomassini et al., 2004) methodological issues and conflicting results have prevented any final conclusion on effectiveness. A Cochrane systematic review concluded that the efficacy of amantadine in treating MS fatigue is poorly documented and emphasized the need for good quality randomized controlled trials. (Pucci et al., 2007) The most commonly reported adverse effects in reviewed trials were mild nausea and dizziness that did not require treatment. (Ledinek et al., 2013; Pucci et al., 2007; Shaygannejad et al., 2012) Considering its relative safety, wide availability and conflicting evidence for efficacy, we chose amantadine as a comparator in this study.

5.1.2. Modafinil: Modafinil is a non-amphetamine wake-promoting agent that is FDA-approved for treatment of narcolepsy, obstructive sleep apnea and shift work sleep disorder. (Lange et al., 2009) Its mechanism of action is not clear; however, it is believed to have dual noradrenergic and dopaminergic properties and increase cortical activity in the frontal lobes. (Kumar, 2008) Modafinil is the most frequently prescribed fatigue medication, as reported by patients participating in a global registry of for MS research, treatment, and patient education (NARCOMS). (Hadjimichael et al., 2008) Three randomized controlled trials produced inconsistent results regarding the beneficial effects of modafinil in MS fatigue. While two randomized trials reported no effects, (Ledinek et al., 2013; Stankoff et al., 2005) another trial reported clear benefits. (Lange et al., 2009) A systematic review of the effect of modafinil in treatment of fatigue in MS and several other neurological disorders concluded that clinical trials have provided inconsistent results. (Sheng et al., 2013) the most common treatment-related adverse effects included headache, nervousness and nausea. (Mitler et al., 2000) Because modafinil is widely used in clinical practice to treat MS-related fatigue and is safe and relatively well-tolerated; we chose it as a comparator in our pragmatic randomized controlled trial.

5.1.3. Methylphenidate: Psychostimulants have also been used for treatment of fatigue in different chronic conditions. Methylphenidate is an amphetamine like psychostimulant approved for the treatment of ADHD. It increases the level of monoamines in the synaptic cleft by enhancing their release and blocking their reuptake. Common adverse effects associated with methylphenidate include headaches, nervousness, irritability, tremor, insomnia, anorexia, gastrointestinal upset and heart palpitations. (Mitler et al., 1994) The risk of addiction is relatively low (less than 1-3%). (Bassetti and Aldrich, 1996) Methylphenidate has been tried in several randomized controlled trials of fatigue treatment in conditions other than MS. (Breitbart et al., 2001; Cueva et al., 2012; Escalante et al., 2014; Kerr et al., 2012) Interestingly, the results of those trials have also been conflicting. Despite lack of rigorous evidence, methylphenidate is one of the commonly used and recommended medications for the treatment of fatigue in MS. (Krupp and Christodoulou, 2001)

The only randomized controlled trial of psychostimulants in MS fatigue was performed using pemoline; a medication used for treatment of attention deficit hyperactivity disorder (ADHD). (Weinshenker et al., 1992) This study concluded that pemoline may be an effective short-term treatment for MS fatigue, but is not well-tolerated by many patients. This medication is however currently not available in the US. The results of the trials of different doses of pemoline were also inconsistent. (Krupp et al., 1995; Weinshenker et al., 1992)

Because psychostimulants are widely used for treatment of fatigue in MS and other chronic conditions, after consultation with several other neurologists and patients with MS, we decided to include an amphetamine-like stimulant as a comparator in our trial. We chose methylphenidate as a comparator, because it has been tried in several clinical trials of fatigue treatment (in conditions other than MS) and is an extensively used medication (for treatment of ADHD) with well-known side-effect and safety profiles and is inexpensive.

In summary, amantadine, modafinil and methylphenidate are FDA-approved for the treatment of several neurological conditions and have been on the market for many years. Because they have been most commonly studied for MS fatigue, and their safety profile is well known, we will assess and compare their effectiveness in MS-related fatigue in a group of patients representative of the MS population in the US. Based on unclear efficacy of these medications, we concluded that the proposed trial should include a placebo treatment period. To compare the effectiveness of these medications against each other requires showing they are superior to placebo in the first place. In the proposed study, we will be powered to demonstrate the superiority of one (or more) of these medications to placebo and compare their efficacy against each other.

5.2. Treatment arms

Using a balanced Latin-square crossover design, subjects will be allocated, in a double-blind, randomized fashion, to one of the four treatment sequences (Figure 1): 1) amantadine, placebo, modafinil, methylphenidate; 2) placebo, methylphenidate, amantadine, modafinil; 3) modafinil,

amantadine, methylphenidate, placebo; and 4) methylphenidate, modafinil, placebo and amantadine (Figure 1). Each treatment period will be 6 weeks and there will be minimum of a 2-week washout period between each treatment period.

5.3. Treatment assignment

Patients will be randomly assigned to one of the above mentioned treatment sequences in approximately a 1:1:1:1 ratio. The assigned study statistician will generate the randomization schedule and send this information to the dispensing pharmacy that will prepare and distribute the drug packages to UCSF and JHU MS centers.

5.4. Treatment blinding

Treatment sequence assignment will be blinded.

Research coordinators, and research nurse will remain blinded to the treatment sequence assignment from the time of randomization of the first patient until database lock.

Pharmacist at Johns Hopkins and UCSF and the study manager will not be blinded to treatment assignment. To help the participants and their treating physicians to choose the medication that was the most helpful to them during the clinical trial; the study pharmacist will unblind the participants after they finish all the study procedures by sending them an email. If, requested by a participant at the end of participation in the study and finishing all study procedures, the study nurse (or the site coordinator) will send the participant his/her completed questionnaires (including the baseline questionnaires and all the end-of-medication-period questionnaires). The study nurse (or the site coordinator) will remain blinded to the study medication assignment.

5.5. Treating the patient

5.5.1. Patient numbering

Each patient will be uniquely identified in the study by a combination of her/his center number (1000 for UCSF and 2000 for JHU) and patient number. Upon signing the informed consent form, the patient is assigned a patient number by the site PI or study team member. At each site, the first patient screened is assigned patient number 1 (e.g. 1001 or 2001), and subsequent screened patients are assigned consecutive numbers. Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomized, the reason for not being randomized will be entered in the screening log.

5.5.2. Dispensing the study treatments

Study medications will be distributed before each treatment period. They will be sent to participants' mailing address through overnight FEDEX. Study medications will be mailed either before the baseline assessment (for the first treatment period) or during the washout periods between the treatment periods (for the second, third and fourth treatment periods). For the first treatment period, if the participant's eligibility is confirmed while s/he is still at the screening visit, the study team can randomize the participant and dispense the first period medication to

the participant. Clinical research coordinator at each site will be responsible for dispensing study medications.

5.5.3. Supply, storage and tracking of the study treatments

Study medications will be compounded by the University of Iowa Pharmaceuticals. Study medications will be provided as capsules. During each study period, participants will receive a bottle containing orange/red colored capsules and a bottle containing blue colored capsules. This plan is designed to keep the titration schedule for all treatment periods the same and keep participants and evaluators blinded to treatment assignment.

For amantadine treatment period, orange/red colored capsules will contain amantadine 100 mg and blue colored capsules will contain inert substance (placebo).

For modafinil treatment period, orange/red colored capsules will contain modafinil 100 mg and bluecolored capsules will contain inert substance (placebo).

For methylphenidate treatment period, both orange/red colored and blue colored capsules will contain methylphenidate 5 mg.

For placebo treatment period, both orange/red colored and blue colored capsules will contain inert substance (placebo).

The pharmacy will compound and supply study medications for the next six months of projected recruitment. Study medications will be bottled and labeled (according to the randomization table produced by the statistician) and will be shipped to each study site. Eight labeled bottles will be assigned to each participant (two bottles per study period, one containing orange/red colored capsules and one containing blue colored capsules). Study medications will be stored at each site according to pharmacy instructions.

5.5.4. Instructions for prescribing and taking study treatments

Study medications will be titrated according to the Figure 2.

During all treatment periods, participants will start taking one orange/red colored capsule in the morning for one week. At week two, participants will take one orange/red colored capsule and one blue colored capsule in the morning. Beginning at week three, participants will take one orange/red colored capsule and one blue colored capsule in the morning and one orange/red colored capsule in the early afternoon. Beginning at week four, participants will take one orange/red colored capsule and one blue colored capsule in the morning and one orange/red colored capsule and one blue colored capsule in the early afternoon. Week five dosing schedule will be similar to week four. Beginning with week six, participants will taper the dosage and will take one orange/red colored capsule and one blue colored capsule in the morning.

The above dosing schedule will be followed by participants who can tolerate the medication and dose titration. If the participants tolerate the study medications without developing any side effects, they will be allowed to titrate the medication according to the above schedule, even if

they do not receive such instructions from the study nurse. Those participants who develop new or worsening symptoms, are not allowed to titrate the medication before receiving such instructions from the study nurse. The study nurse will call or get in touch with each participant (through email or text) at least five times during each treatment period and will inquire about participants' development of adverse events, tolerability of medication and if they can tolerate an increase in the dose. The schedule of nurse phone calls and the algorithm for dealing with participants' issues regarding medication titration is depicted in Table 1 and Figure 3 (attached at the end of the document), respectively.

Table 1. Schedule of research nurse phone calls. Please note that the participants can be contacted ±3 days from the days shown in this table.

	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday	Monday
Week 1	Start med						1st phone call
Week 2							2nd phone call
Week 3							3rd phone call
Week 4							
Week 5	4th phone call for reminding or administering the end-of-period questionnaire and asking about adverse event and tolerability						5th phone call (for tapering the medication)
Week 6							

5.5.5. Concomitant treatment

Participants will be instructed to notify the study site about any new medications they take after the start of study medications. All medications and significant non-drug therapies (including physical therapies and blood transfusions) administered after the participants start study medications must be listed on the concomitant medications form on the CRF.

5.5.6. Discontinuation of study treatments and premature patient withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator team will make every effort to determine the primary reason for a participant's premature withdrawal from the study and record this information.

If a participant decides to stop the study medication or because of development of adverse events, is instructed by the study team to stop the study medication, the outcome measures of that particular period will be performed during the 5th week of that medication period (i.e. at the scheduled time frame). If the participant is continuing the study and is willing to start the study

medication of the next period, as long as they have been off the study medication for at least two weeks and they have answered the outcome questionnaires on week 5, the medication period can be started immediately. If a participant decides to drop out of the study, stop the study medication and start a medication outside of the study, the outcome questionnaires should be administered while the patient is still on the study medication or before they start a medication outside of the study.

Study drugs must be discontinued for a given participant if the investigator determines that continuing it would result in a significant risk for that participant. The following events/conditions may be considered sufficient to support a decision about the study medication discontinuation in individual cases:

- Serious adverse event

- Withdrawal of consent

- Pregnancy

Participants who discontinue study medications should not be considered withdrawn from the study, unless one of the reasons listed above for study withdrawal are met.

The date and primary reason for study drug discontinuation should be recorded.

5.5.7. Study completion

The study will be considered completed for an individual participant when he/she completes all four treatment periods, or earlier in case of premature study discontinuation. The study as a whole will be considered completed when all enrolled participants have completed the study.

5.5.8. Role of site personnel

- Bardia Nourbakhsh, MD, MAS, Principal Investigator: Dr. Nourbakhsh is an assistant professor in the department of Neurology at JHU. He will oversee the overall conduct of the entire research project. He has been involved in designing clinical trials of symptomatic treatment in MS for the past few years and has completed formal education in epidemiology, biostatistics and trial design as part of the UCSF Masters' in Clinical Research. He will work closely with Dr. Waubant, the study co-PI and site PI at UCSF. He will be responsible for drafting the study protocol, recruiting participants in the study at JHU and reviewing their eligibility. He will perform full neurological examination (EDSS) at the screening visit for JHU patients. He will also supervise the JHU research nurse. He will lead monthly teleconferences with Hopkins and UCSF study team members. He will have twice a month telephone meetings with the UCSF study manager and JHU research nurse to review the progress of the study at all sites. He will identify issues related to recruitment and retention in the study to address them in a timely manner. He will oversee the overall quality control and safety of the study. He will be responsible for attending to and collaborating with the Study Advisory Committee. He and the study manager will prepare a quarterly report for submission to the DSMB. He will work with

Drs. Waubant for data collection and analysis, and preparation of reports and manuscripts. He will prepare the scientific reports for collaborative review, present data at scientific meetings and be a major contributor to writing and submitting related manuscripts.

- Bridget Morris, RN, BSN JHU Research Nurse:
- She will be responsible for weekly phone calls to all participants, recruited at either JHU or UCSF, inquiring if they experienced any side effects, collect side effects in source documents. Under the supervision of Dr. Nourbakhsh at JHU, she will ensure that subjects tolerate titration of study drug and will guide them on how to titrate the medication. She will also answer patients' clinical questions that arise during the trial. She will bring up medical issues to the attention of the site PIs. She will document the outcomes of her phone calls (including reports of adverse effects and serious adverse effects and maximum tolerated dose).
- She will explain the study and related processes to the subjects, and consent them for the study at JHU. She will be the primary subject contact for this study at JHU. She will also prepare IRB-approved letters that will be sent to physicians who usually refer patients to the center for clinical trials and will be the first-line of contact for these physicians who want to refer patients to the study. She will schedule study visits and return subjects phone calls. She will work with the MS clinic to identify potential candidates for the study. She will enroll subjects at JHU, collect data, and perform data entry and cleaning. She will meet twice a month with Drs. Nourbakhsh and Waubant, and the UCSF study manager to review study progress and potential issues. She will work with the pharmacy to dispense the study medications. She will reconcile shipments of study drug to subjects and remind subjects about completing necessary testing that is part of the primary and secondary outcomes.

- Emmanuelle Waubant, MD, PhD, Co-Principal Investigator: Dr. Waubant is a Professor of Neurology at UCSF. Dr. Waubant has extensive experience in the design and execution of clinical trials of anti-inflammatory, neuroprotective and symptomatic treatments in the field of MS, including treatment of MS fatigue. Along with Dr. Nourbakhsh, she will oversee the conduct of the trial at UCSF and Hopkins. She will also recruit patients in the study, perform neurological examination (EDSS) on participants recruited at UCSF. She will be attending monthly teleconferences with UCSF and Hopkins study team members, pertaining to enrollment and retention. She will meet twice a month with the UCSF study manager and study coordinator to review progress with the trial and review issues and ways to troubleshoot these in a timely manner. She will work with Dr. Nourbakhsh for data collection and analysis, and preparation of reports and manuscripts.

- Nisha Revirajan, UCSF Study Manager: Dr. Revirajan is an experienced study coordinator who has been working with Drs. Nourbakhsh and Waubant over the past few years on several industry-sponsored and investigator-initiated trials. She will explain the study and related processes to the subjects, and consent them for the study at UCSF in conjunction

with the UCSF study coordinator. She will be the primary subject contact for this study at UCSF. She will also prepare IRB-approved letters that will be sent to physicians who usually refer patients to the center for clinical trials and will be the first-line of contact for these physicians who want to refer patients to the study. She will schedule study visits and return subjects phone calls. She will work with the MS clinic to identify potential candidates for the study. She will enroll subjects at UCSF, collect data, perform data entry and cleaning. She will meet twice monthly with Drs. Nourbakhsh (through teleconference) and Waubant, and the study team at UCSF and JHU to review study progress and potential issues. She will work with the pharmacy to dispense the study medications. She will reconcile shipments of study drug to subjects and remind subjects about completing necessary testing that is part of the primary and secondary outcomes.

- TBN, UCSF Study Coordinator: She will explain the study and related processes to the subjects, and consent them for the study at UCSF. She will be scheduling and returning patients phone call. She will work with the MS clinic to identify potential candidates for the study. She will enroll subjects at UCSF, collect data, perform data entry, provide data cleaning for clinical and demographic data. She will provide time for data entry as necessary and will participate in teleconferences. She will work with the pharmacy to dispense the study medications.

- Charles McCulloch, PhD, Statistician: He will be responsible for drafting of statistical methodology of the study protocol and overseeing the preparation of the randomization protocol in the first year and working with the pharmacist at both sites for the execution of randomization protocol. He will work with Drs. Nourbakhsh and Waubant to finalize the plan of data analysis and help with the preparation of DSMB reports. He will oversee the final analysis of the data at the end of the trial and report. Working with the junior statistician, he will prepare a complete and clean dataset for sharing upon request, and will participate to the preparation of manuscripts related to the study.
- TBN, Junior Statistician at UCSF: S/he will work with the senior statistician to write the analysis plan. S/he will be responsible for setting up the RedCap database, preparation of case report forms, database troubleshooting, monitoring data accrual, auditing missing data, and monitoring recruitment. S/he will participate in generating DSMB reports by auditing the database, locking the database and performing analyses (if required by the protocol). When the data collection is complete, s/he will be responsible for database cleaning and locking, performing the analyses and preparing results (supervised by the senior statistician).

Recruitment, visit schedule and assessments (Table 2)

Recruitment: Eligible subjects with MS will be recruited from the Johns Hopkins MS Center, at which over 3,000 MS patients, who come from diverse racial/ethnic and socioeconomic

backgrounds and from a wide catchment area, are seen annually. We will also screen potentially eligible subjects using an IRB-approved Telephone Screening Script. This will allow us to screen patients who may or may not meet the study's eligibility criteria. If a patient meets the eligibility criteria via telephone screening, we will schedule the patient to come in for a baseline visit. The study coordinator will call only patients of physicians on the study team.

Screening visit: This will be the only in-person study visit. Because an MFIS score lower than the threshold specified in the inclusion criteria is one of the most common reasons for screening failure, we will use an oral consent process to administer the MFIS test. If the patient's MFIS score is in the acceptable range, PI or designee will explain the study consent to study participants, and the rest of the study visit assessments will occur after the study participants sign the consent form. Screening visit procedures include review of eligibility criteria, physical exam, EDSS, collecting vitals, and labs, and completion of MFIS, Neuro-QoL fatigue item bank and screening for depression by completing HADS-depression subscale. If physical examination and/or EDSS is performed by one of the neurologists in the participating centers (JHU or UCSF) during a clinical encounter in three months prior to the screening visit and the results were available for review at the time of screening, there is no need to repeat them and we will use those data during the screening. The screening labs will be collected if the screening visit MFIS score is >33. If the required labs were done in 30 days prior to screening and the results were available for review at the time of screening, there is no need to repeat the labs (except the urine pregnancy test). Study participants will be enrolled into the study after the study physician confirms participants' eligibility to move forward with the study. We will notify the study participants about their eligibility before planning the baseline fatigue assessment. Participants will be randomized to one of the 4 study sequences (Figure 1) within 60 days from the screening visit.

After randomization: The study drug of the first assigned period will be mailed to the participant. Alternatively, if a participant's eligibility is confirmed while s/he is still at the screening visit, the study team can randomize the patient and dispense the first period medication to the participant The baseline values of the primary and secondary endpoints of the study will be obtained through remote answering (web based, phone or mailed paper forms) within three days before starting medications. Participants will start taking the study medication of the first period of their assigned sequence within 60 days after the screening visit.

Table 2 – The schedule for study procedures and assessments

Tests and assessments	Screening visit	Baseline	Weeks 1-4	Week 5	Weeks 9-12	Week 13	Weeks 17-20	Week 21	Weeks 25-28	Week 29
Informed Consent	X									
Inclusion/exclusion criteria	X									

Medical history	X									
Vital signs	X									
Physical examination	X									
Blood draw (safety labs)	X									
Study drug dispensation		X								
Study medication titration			X		X		X		X	
EDSS	X									
MFIS	X (in-person)	X (web)		X (web)		X (web)		X (web)		X (web)
HADS Depression subscale	X									
Neuro-QoL fatigue item	X	X		X		X		X		X
Epworth Sleepiness Scale (ESS)	X	X		X		X		X		X
Going forward, would you choose this medication as your fatigue treatment?				X		X		X		X
Side effects assessment			X	X	X	X	X	X	X	X

6.1. Information to be collected on screening failures

Patients who have signed the informed consent form, but fail to meet eligibility criteria for enrollment, will be deemed screen failures and the reason for failure will be documented on the screening log. Only demographic data, screening MFIS and the reason for screen failure will be collected.

6.2. Patient demographics and other baseline characteristics

Patient demographic characteristic data include date of birth, age, sex, race, ethnicity and employment status. Relevant medical history will include data until the start of the study drugs and will capture pre-existing medical conditions and any concomitant medications taken to treat these conditions. Where possible, diagnoses, and not symptoms will be recorded. MS history, history of fatigue and previous MS and fatigue treatment will also be collected.

6.3. Efficacy

6.3.1. MFIS

The MFIS is a patient-reported outcome that has been proposed by the MS Council for Clinical Practice Guidelines as the instrument of choice for assessing fatigue in MS (PC-3). It has been developed by the National MS Society (NMSS). It is derived from the 40-item Fatigue Impact Scale (FIS) and is a component of the MS quality of life inventory (MSQLI). It has 21 items and assesses more dimensions of fatigue than the other fatigue measures: physical (9 items), cognitive (10 items) and psychosocial (2 items). The scale score is the sum of the 21 items and higher score indicates more severe fatigue. The maximum score is 84. The scale has shown good reproducibility, ease of use and good correlation with the Fatigue Severity Scale (FSS) scores. (Téllez et al., 2005) The MFIS also probably measures cognitive and psychosocial aspects of fatigue better than the FSS. A cut-off value of 38 distinguishes fatigued from non-fatigued MS patients. (Flachenecker et al., 2002) The NMSS has recognized MFIS as a valid and reliable measure of the impact of fatigue on activities of daily living in patients with MS. (Téllez et al., 2005) A Spanish version of the MFIS has been developed and no cultural or linguistic differences were found in the psychometric properties of the Spanish version in patients with MS. (Kos et al., 2005) The MFIS has been used as an endpoint in multiple clinical trials. (Gillson et al., 2002; Rammohan et al., 2002; Schwid et al., 2003; Stankoff et al., 2005) The MFIS can be easily administered in-person, over the web and on the phone and requires minimal or no guidance. Answering the questionnaire is possible in less than 5 minutes.

6.3.2. Neuro-QOL fatigue item bank

Neuro-QoL: Quality of Life in Neurological Disorders (Neuro-QOL) project was commissioned by the National Institute of Neurological Disorders and Stroke and has developed psychometrically robust and clinically relevant health-related quality of life measures applicable across neurological conditions. (Cella et al., 2012; Gershon et al., 2012) The psychometric properties of Neuro-QoL have been assessed in MS. (Cook et al., 2015; Miller et al., 2015) The Neuro-QoL fatigue item bank is comprised of up to 19 items with a maximum total score of 95. Higher scores indicate more severe fatigue impact. This patient-reported outcome can be answered in-person, over the web or on the phone in less than 5 minutes.

6.3.3. Epworth Sleepiness Scale (ESS)

ESS is a frequently used measure of patient-reported sleepiness in clinical neurology and sleep medicine. Sleepiness might be mistakenly considered synonymous with fatigue, however, there is complex relationship between these two conditions. Sleep problems might contribute to both daytime sleepiness and fatigue. Some of the prescribed medications for the treatment of fatigue (including modafinil and methylphenidate) have confirmed efficacy and FDA-approval for treatment of sleep disorders. Using ESS, we can analyze the differential effect of the study mediations on fatigue and sleepiness.

ESS is a list of eight situations in which participants rate their tendency to fall asleep on a scale of zero to three. The total score is based on a scale of zero to 24.

6.3.4. Single question regarding treatment satisfaction

We will ask the participants at the end of each treatment period a question regarding their satisfaction with the treatment:

"Taken into consideration the possible benefits and/or disadvantages of this medication, would you choose it, going forward to treat your MS fatigue?"

Participants will answer to this question yes or no.

6.4. Safety and tolerability

The safety outcome will be analyzed by including all subjects who have received at least one dose of study medication. Participants will be analyzed according to the actual treatment received. The assessment of safety will be based on the frequency of adverse events. Tolerability of medications will be reported as the range, median and average highest tolerated dose for each medication.

7. Safety monitoring

The study medications have known safety profiles and are already FDA-approved and marketed for other indications. There is no requirement for routine blood work for these medications in clinical practice. Hence, in this pragmatic and real-world clinical trial, we will have no required in-person clinical exam or laboratory testing for detection of adverse events; however, we will collect patient-reported adverse events.

7.1. Adverse events

An Adverse event (AE) is the appearance or worsening of any undesirable sign, symptom or medical condition occurring after the start of the study medications, even if the event is not considered to be related to study drug.

The occurrence of AEs will be sought by non-directive questioning of the participant at each telephone encounter. All patient-reported AEs must be recorded with the following information:

- The severity grade (mild, moderate, severe)

- Its relationship to the study medications (suspected/not suspected)

- Its duration (start and end dates)

- If it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening

- results in persistent or significant disability

- constitutes a birth defect/congenital abnormality

- requires inpatient hospitalization for at least 24 hours or prolongation of existing hospitalization for at least 24 hours. Pre-planned, elective hospital admissions are not considered SAEs.

- is medically significant

All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken; study drug dosage adjustment; study drug permanently discontinued; concomitant medication given; non-drug therapy given; patient hospitalized.

7.2. Pregnancies

Female participants of child-bearing potential will have a urine pregnancy test at the screening visit and will be informed of the need for effective contraception to prevent pregnancy while participating in the study. Contraception must be used during the study and one month after stopping the last study medication.

7.4. Data and Safety Monitoring Board (DSMB)

The DSMB will be an external board comprised of one internist, one MS clinician, and one biostatistician (names to be determined). Before the start of the trial, the DSMB must review and approve the study protocol. Study PI, statistician and manager will prepare a report of all safety data before DSMB meetings. The DSMB will meet by teleconference every six months or sooner if severe AEs are brought to their attention by the study PI. They will make recommendations to ensure patients' safety in the trial. Because of the nature of the study and the medications used, there is no need to set early stopping rules for futility or unequivocal evidence of efficacy or harm.

8.Database management

8.1. Data collection

We will use REDCap (Research Electronic Data Capture) [https://projectredcap.org/], a secure web application to build and manage online surveys and databases, collect data, create the trial database and access the data for analysis. Most of the trial data (including screening and baseline

values of MFIS and questionnaires answered in each study period by the participants will be directly captured via REDCap forms. If participants cannot enter data online, they will complete a paper form and mail it to study coordinator who will do data entry. Alternatively, the study coordinator will call the subject who will answer questions on the phone, and data will be entered at that time by the study coordinator. Study coordinator will enter the data required by the protocol into the Electronic Case Report Forms (CRFs). Junior statistician will be responsible for setting up the RedCap database, preparation of case report forms, database troubleshooting, monitoring data accrual, auditing missing data, and monitoring recruitment. The site PIs will assure that the data entered into CRFs are complete and accurate.

8.2. Database management and quality control

Junior statistician and study manager will review the data entered into CRFs by the study coordinators for completeness and accuracy and instruct them to make any required corrections or additions.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis.

9. Data analysis

The statistical models specified in this section may be modified by including fewer covariates in the models in case the pre-specified models do not converge.

9.1. Analysis sets

Efficacy set: The efficacy set comprises all participants who have at least the primary outcome measured in one treatment period. Following the intention-to-treat (ITT) principle, participants will be analyzed according to the randomized sequence assignment, even if they actually received the medications in a different sequence. This method will also be used for the secondary efficacy endpoint.

Safety Set: The safety set includes all patients who received at least one dose of study medication. Subjects will be analyzed according to the actual treatment received. The Safety Set will be used for all safety analyses.

9.2. Patient demographics and other baseline characteristics

Patient demographics and other baseline characteristics, will be summarized using frequency distributions (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

Background information includes MS subtype, prior medication, past/current medical conditions, duration of the disease, baseline fatigue level and baseline EDSS.

9.3. Analysis of the primary and secondary outcomes

9.3.1. Primary and secondary efficacy outcomes

Primary efficacy outcome: MFIS at the end of each treatment period.

The MFIS is a patient-reported outcome that has been proposed by the MS Council for Clinical Practice Guidelines as the instrument of choice for assessing fatigue in MS. It has been developed by the National MS Society (NMSS). It is derived from the 40-item Fatigue Impact Scale (FIS) and is a component of the MS quality of life inventory (MSQLI). It has 21 items and assesses more dimensions of fatigue than the other fatigue measures: physical (9 items), cognitive (10 items) and psychosocial (2 items). The scale score is the sum of the 21 items and higher score indicates more severe fatigue. The maximum score is 84. The scale has shown good reproducibility, ease of use and good correlation with the Fatigue Severity Scale (FSS) scores. (Téllez et al., 2005) The MFIS also probably measures cognitive and psychosocial aspects of fatigue better than the FSS. A cut-off value of 38 distinguishes fatigued from non-fatigued MS patients. (Flachenecker et al., 2002) The NMSS has recognized MFIS as a valid and reliable measure of the impact of fatigue on activities of daily living in patients with MS. (Téllez et al., 2005) A Spanish version of the MFIS has been developed and no cultural or linguistic differences were found in the psychometric properties of the Spanish version in patients with MS. (Kos et al., 2005) The MFIS has been used as an endpoint in multiple clinical trials. (Gillson et al., 2002; Rammohan et al., 2002; Schwid et al., 2003; Stankoff et al., 2005) The MFIS can be easily administered in-person, over the web and on the phone and requires minimal or no guidance. Answering the questionnaire is possible in less than 5 minutes. The MFIS questionnaire is attached in the appendix section.

Secondary outcome: Neuro-QoL fatigue item bank score and ESS score at the end of each treatment period.

9.3.2. Statistical model, hypothesis and method of analysis

The null hypothesis for the primary endpoint is that the MFIS scores at the end of all medication periods (including placebo) are equal. We will use a linear mixed-effect regression model with the primary outcome of the study (MFIS score obtained while taking maximal tolerated or target dose in each treatment period) as the independent variable, and the study medication, treatment sequences, treatment periods and study sites as the fixed effects with the subjects as the random effect. The least-square means and associated standard errors will be calculated for each study medication. Fisher's least-significant-difference method will be used to calculate multiple comparisons among medications. According to this method, the overall and global difference between study medications will be tested in the mixed-effect model. If this test is significant at 0.05 level, we will make pairwise comparisons between study treatments using estimated contrast at 0.05 level. In a sensitivity analysis, we will check the presence of the first-order

carryover effect (by adding it to the model as a fixed effect). The secondary efficacy outcome will be analyzed using a similar mixed-effect model.

9.3.3. Handling of missing values and discontinuations

To minimize missing data, we have simplified the process of data collection. Instead of trying to collect as much information as possible, we have focused on the main research objective which is to determine if any of the study medications will improve fatigue and if this improvement in fatigue is associated with better quality of life. As such, only measures of fatigue and fatigue-related quality of life are being considered as efficacy outcomes in this study. This will prevent imposing any unnecessary burden on study participants and allows us to dedicate more resources to maximize the quality of data collection. The outcomes of the study will be collected while the participants are at home or work place, with no need for in-person visits after the screening visit. The questionnaires are relatively short and can be answered quickly and easily by the subjects. Subjects will receive electronic reminders on the days they are supposed to report fatigue severity. Study personnel will be actively engaged during each treatment period with contacting the participants to review drug tolerability and guiding titration. This will likely improve patient participation and retention that in turn will decrease missing data.

Study coordinators will contact subjects who have not reported fatigue severity or those who have decided to stop study medication to inquire about the reason of the missing values or dropout. With the participants' consent, we will continue to collect data, even if they decide to stop taking the study medication. Using data from a similarly designed crossover clinical trial (Gilron et al., 2005), we estimated a conservative 20 % dropout between each treatment period and accounted for it in the sample size calculation. The proportion of patients who drop out of the study and the recorded reasons will be presented in the manuscript reporting the results of the trial.

Our pre-specified primary analysis model, the linear mixed-effects model with maximum likelihood method, will allow handling of missing data in several treatment periods.

We will run several pre-specified sensitivity analyses to explore the effect of missing data on the results of the trial. The first sensitivity analysis will assume that the missing data can be modeled based on observed data (i.e. data "missing at random"). We will then utilize the multiple imputations method for missing values. Multiple imputations using a linear mixed-effects regression model will be conducted 50 times with a random seed pre-specified to generate 50 analysis datasets. The mixed-effects model used for the primary analysis will also be used to analyze each of the 50 data sets. Using Rubin's rule (Rubin, 1996), we will then combine the estimates, standard error of the estimate and the p-values to provide the final reference results. In another sensitivity analysis, we will substitute the missing values with the highest fatigue score recorded during the trial, assuming severe fatigue is associated with missingness.

9.4. Safety and tolerability outcomes

The safety outcome will be analyzed by including all subjects who have received at least one dose of study medication. Participants will be analyzed according to the actual treatment received. The assessment of safety will be based on the frequency of adverse events. Tolerability of medications will be reported as the range, median and average highest tolerated dose for each medication.

9.5. Assessment of heterogeneity of treatment effect

Our pragmatic trial, with broad eligibility criteria, will help generate evidence that will be generalizable. However, stakeholders (e.g. patients and clinicians) are also interested to know how well a treatment is likely to work for an individual. As such, assessing the heterogeneity of treatment effect is critical to understand the applicability of the results in individual patients. This issue is relevant for efficacy endpoints as well as safety and tolerability. We plan to assess the heterogeneity of treatment effect in the proposed trial and will explore the possibility of differences in efficacy, safety and tolerability of a specific study medication in a pre-specified subgroup of participants. Although our trial is powered to detect an average treatment effect, we will investigate effect modification by several baseline covariates as outlined below.

A) Subjects with relapsing-remitting versus progressive MS: Although the exact pathological processes at play in progressive forms of MS are unknown, they are hypothesized to be different from relapsing-remitting forms and involve more extensively changes in the innate immune response. The most convincing evidence for this difference is the fact that FDA-approved disease-modifying treatments for relapsing MS do not prevent progression of disability in progressive MS. (Ontaneda et al., 2015) The severity of fatigue is also different between these two groups. A recent study reported that patients with primary or secondary progressive disease have two and a half time the odds of severe fatigue compared to patients with the relapsing-remitting type. (Weiland et al., 2015) The difference in the pathophysiology and fatigue severity between the 2 forms of MS raises the possibility of a differential response to drugs targeting fatigue.

B) Subjects with versus without depression: Fatigue and depression are both common symptoms associated with MS. They are also very highly associated with each other. In one report, patients with clinically significant fatigue were 9 times more likely to screen positive for depression. Of those who screened positive for depression, 92.9% had clinically significant fatigue. (Taylor et al., 2014) Although the causal relationship of this association is not clear, it is conceivable that the response to fatigue treatment might be different between subjects with and without depression. However, because most fatigued subjects will have depression, there may be very few in the trial without depression. This issue may affect the assessment of effect modification by depression.

   To screen for depression, we will use Hospital Anxiety and Depression Scale (HADS), depression

subscale. This is a validated measure of depression in patients with MS and cutoff score of 11 has high sensitivity and specificity to detect depression. (Watson et al., 2014)

C) Subjects on disease-modifying treatments versus those who are not: Disease-modifying treatments reduce inflammatory disease activity (i.e. relapse rate and MRI changes) in patients with relapsing MS; however, their effect on fatigue is not clear and remains a controversial issue.(Metz et al., 2004; Putzki et al., 2008, 2009; Wilken et al., 2013) It is a fair plan to explore the differential effects of anti-fatigue medications in those who do and those who do not receive disease-modifying treatments.

D) Subjects with mild degrees of disability (EDSS<3.0) versus more severe disability (EDSS>=3.0): The association of fatigue and neurological disability also remains controversial.(Koch et al., 2009; Pittion-Vouyovitch et al., 2006) In our cohort of patients with early relapsing disease, we found a strong cross-sectional and longitudinal association between severity of fatigue (as measured by MFIS) and neurological disability (as measured by EDSS and MSFC). On longitudinal evaluation, each 0.5-point increase in EDSS was associated with 3.4-point increase in MFIS 95% CI:1.4 – 5.5, p=0.001) and each 0.1 decrease in MSFC was associated with 0.5-point increase in MFIS (95%CI:0.1 – 0.9, p=0.009). (unpublished data, manuscript in preparation). Based on our strong preliminary data, we hypothesize that the effect of fatigue treatment may be different across different levels of disability which we will explore in heterogeneity of treatment effect analyses.

   Expanded Disability Status Scale (EDSS) is the most commonly used scale for assessing the level of disability in patients with MS.(Kurtzke, 1983) It provides a total score that ranges from 0 to 10. Higher scores indicate more severe disability.

To evaluate the heterogeneity of treatment effect, we will test the multiplicative interaction between treatment effect and each of the above-mentioned subgroup variables. If the statistical test for multiplicative interaction is significant at 0.15 level, we will further explore treatment effect in particular subgroups by stratification.

We will report all pre-planned subgroup analyses, including the previously mentioned four interaction tests and stratified analyses.

9.6. Sample size calculation

Although statements such as “clinically meaningful” or “clinically relevant” changes in MFIS score have been used in a number of studies, no data have been published regarding what MFIS changes reflect objectively.(Larson, 2013) In a study reported by Kos et al., a 10 point or more change in MFIS score was considered to be clinically relevant.(Kos et al., 2007) In our prior trial

of modafinil in MS fatigue(Stankoff et al., 2005), the mean change in each treatment group during the study was almost 10 points, which likely reflects the variability of the measure, and the fact that a lesser change is likely not meaningful. In our cohort of 43 patients with very early MS in a neuroprotection trial (Waubant et al., 2014), frequent measurements of MFIS were obtained for up to 3 years: we found a between-subject variance of 330 and within-subject variance of 80 with an intra-class correlation (ICC) of 0.80 (95% confidence interval of 0.70 to 0.88) (unpublished results). Using more conservative ICC of 0.7, power of 90% and type one error of 0.05 (Bonferroni corrected for 6 pairwise comparisons), we will need 91 patients to detect at least a 10-point difference in MFIS between the placebo and medication groups. Assuming 20% dropout within each treatment period, the total sample size for the proposed trial will be 136 subjects.

9.7. Interim analyses

We do not expect any of the study medications to have dramatic anti-fatigue effects and outperform other medications, to a point that interim analyses of efficacy would necessitate premature stopping of the trial. Hence, we will not perform interim analyses of efficacy in this study.

10. Ethical considerations

10.1. Regulatory and ethical compliance

The Investigators will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" which affords the greater protection to the individual. It is the mission of the physician to safeguard the health of the people. The study physicians' knowledge and conscience are dedicated to the fulfilment of this mission. The clinical trial will fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guidelines for greater protection to the subject.

The study will be submitted to site IRB for approval prior to enrolling study participants into the study. The IRB will be notified annually about study progress, and all important updates on the study or medically important events associated with the study will be submitted to IRB as the study progresses.

The investigator will establish secure safeguards of confidentiality of research data as described in the current revision of the International Ethical Guidelines for Biomedical Research involving Human Subjects. The Health Insurance Portability and Accountability Act (HIPAA), also known as "The Privacy Rule", has set new standards and regulations to protect patients from inappropriate disclosures of their "protected health information" (PHI) that could cause harm to their insurability, employability and/or their privacy. PHI pertains to any information that can be used to identify an individual which is created, used, or disclosed in the course of providing a health care service, such as diagnosis or treatment. HIPAA does allow for researchers to access and use PHI when necessary to conduct research. The Committee for Human Research will act as the HIPAA-required Privacy Board to review the use/disclosure of PHI for research. The study records

will be identified using subject's study number, and initials to protect the privacy of the study participants. The study team will follow the JHU and UCSF IRB recommendations to protect the privacy of study participants. Study consent will also include the privacy language mandated by the Institution's IRB. Vulnerable populations (including fetuses, neonates, pregnant women, children and prisoners) will not be involved in this study. All members of the research teams at JHU and UCSF have received required training in protection of human subjects in research and will receive refresher courses at intervals based on state and federal policies.

10.2. Informed consent procedures

The study investigators, or a person designated by the investigators will explain the IRB approved study consent to study participants and obtain signed informed consent from each subject. The study participants will be given ample time to review the consent, and are encouraged to ask questions during the consent process. For subjects not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read; an impartial witness should be present during the entire informed consent discussion. After the subject and representative, have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The study participants are encouraged to ask questions about the study during the study participation period. The UCSF study participants will be provided with the California Experimental Subject's Bill of Rights. The investigator or designee must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The study participants will be notified about the new study information during the study participation period, and will be re-consented when applicable. A copy of the signed informed consent form will be given to the subjects for their records.

10.4. Publication of the study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Upon request from clinical or research community, a complete, de-identified copy of the final dataset used for the final analyses will be made available within one year after the completion and publication of the study results. The dataset will be sent electronically through secure portals. In addition, we will also explore how data could be made available to investigators around the world through other channels such as the NIH or the National MS Society or other types of websites allowing data sharing.

11. Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Any change or addition to the protocol can only be made in a written protocol amendment. Only amendments that are required for patient safety may be implemented prior to IRB approval.

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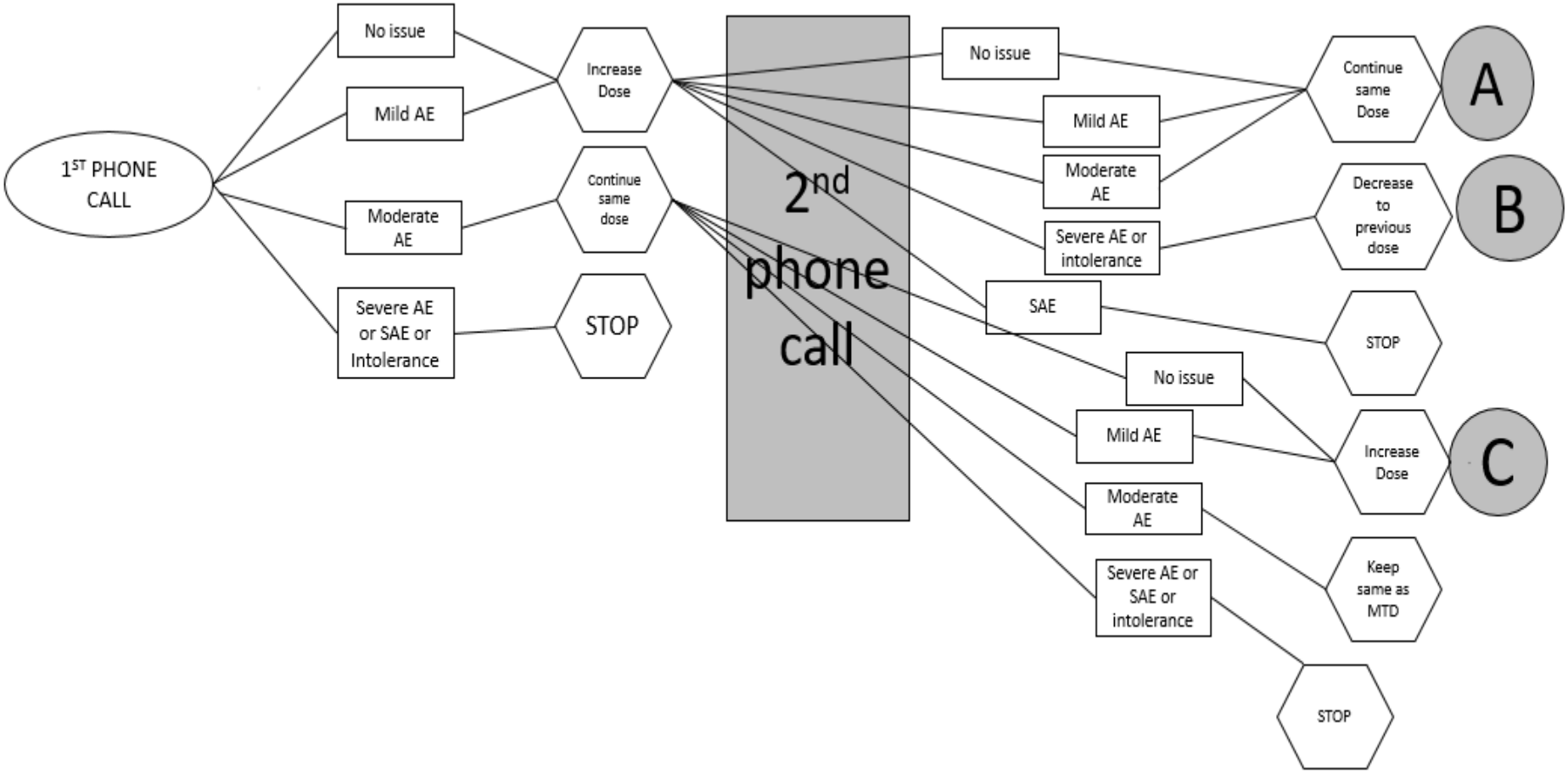
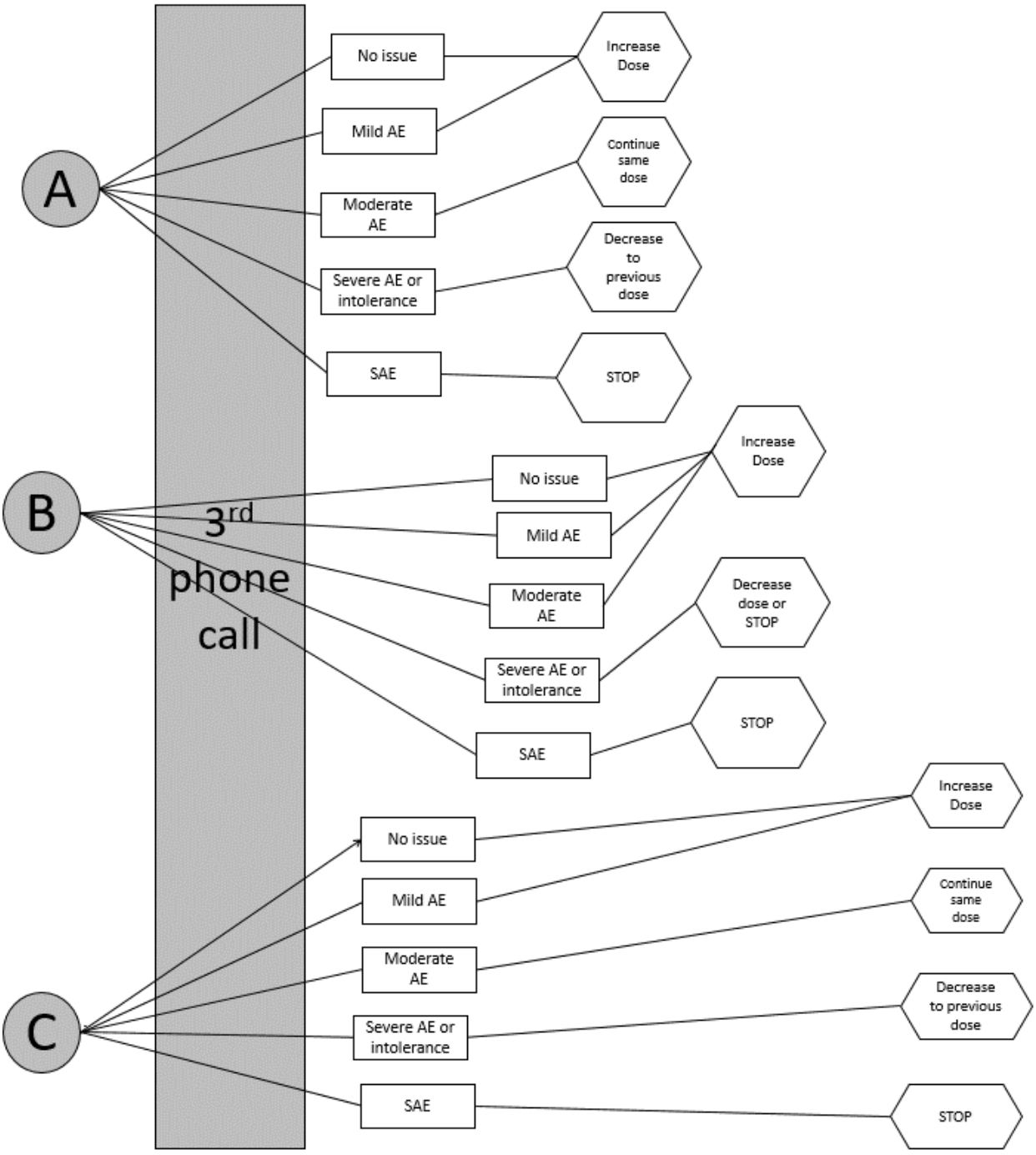
Figure 3- Algorithm to be used by research nurse to address participants' issues during medication titration.


1ST PHONE CALL
No issue
Mild AE
Moderate AE
Severe AE or SAE or Intolerance
Increase Dose
Continue same dose
STOP
2nd phone call
No issue
Mild AE
Moderate AE
Severe AE or intolerance
SAE
No issue
Mild AE
Moderate AE
Severe AE or SAE or intolerance
Continue same Dose
Decrease to previous dose
STOP
Increase Dose
Keep same as MTD
STOP
A
B
C


A
B
C
3rd phone call
No issue
Mild AE
Moderate AE
Severe AE or intolerance
SAE
Increase Dose
Continue same dose
Decrease to previous dose
STOP
No issue
Mild AE
Moderate AE
Severe AE or intolerance
SAE
Increase Dose
Decrease dose or STOP
STOP
No issue
Mild AE
Moderate AE
Severe AE or intolerance
SAE
Increase Dose
Continue same dose
Decrease to previous dose
STOP

Statistical analysis plan for the TRIUMPHANT-MS trial

Design: 4 period, 4 treatment cross-over design.

Data subsets to be analyzed:

1. *Data subset for all efficacy analyses*: The efficacy dataset comprises all participants who have the primary outcome measured in week 5 of at least 1 treatment period. Following the intention-to-treat (ITT) principle, participants will be analyzed according to the randomized sequence assignment, even if they actually received the medications in a different sequence.
2. *Data subset for all safety analyses*: The safety dataset includes all patients who received at least one dose of any study medication. Subjects will be analyzed according to the actual treatment received.

Statistical Analysis Plans:

Efficacy analyses:

1. Outcomes
    a. Primary: MFIS score obtained during week 5 of each treatment period.
    b. Secondary: Secondary outcomes: Neuro-QoL fatigue item bank score and Epworth sleepiness scale during week 5 of each treatment period.
    c. Exploratory: Exploratory outcomes: Subscales of the MFIS during week 5 of each treatment period, the proportion of patients who achieve a minimal clinically important reduction in the MFIS score (compared to the baseline measurement) defined as either a 10 or 14 point reduction (or more).
2. Analyses
    a. We will use a linear mixed-effect regression model (SAS Proc MIXED) in the efficacy dataset for the primary outcome measure utilizing restricted maximum likelihood fitting and Kenward-Roger degree of freedom adjustments. The fixed predictors will be study medication (categorical placebo, Amantadine, Modafinil, Methylphenidate), treatment sequence (categorical 1 to 4), treatment period (categorical 1 to 4), baseline outcome and study site (categorical JHU/UCSF) and subjects as a random effect. If the adjusted test of treatment differences is significant at the α=0.05 level, we will make pairwise comparisons between study treatments using estimated contrasts at the α=0.05 level.
    b. Least squares means, along with 95% confidence intervals will be reported for each drug and the placebo.
    c. The other efficacy outcomes will be analyzed using similar mixed-effect models.
    d. Diagnostic checks

i. Carry-over effects will be assessed by including an additional predictor of treatment in the previous time period (missing for time period 1) and testing its significance at α=0.05
ii. Approximate normality will be assessed by calculating the conditional, studentized residuals and assessing:
    1. Approximate normality of a histogram.
    2. Absence of outliers (as judged by studentized residuals larger than 3 in absolute value) and, if present, their influence of outliers.
    3. A plot of studentized residuals versus predicted values.

e. Heterogeneity of treatment effects
    i. For each of the following potential effect modifiers (all measured at baseline) an analysis will be performed to assess heterogeneity of treatment effects.
        1. relapsing-remitting vs progressive MS,
        2. depression (HADS>11),
        3. on disease modifying treatments (yes/no),
        4. mild vs more severe disability (EDSS<3).
    ii. The analysis will be a repetition of the primary, mixed model analysis but additionally including an interaction of the effect modifier and the treatment effects. If the p-value for interaction is 0.15 or less, subgroup analyses will be conducted within each subgroup defined by the effect modifier.

f. Missing data
    i. We do not expect there to be significant missing data. Furthermore, the use of mixed model analyses provide protection against bias due to missing data. However, if there is significant missing data for any variable (defined as >15%) we will conduct a sensitivity analysis using multiple imputation.

Safety analyses:

1. Outcomes
    a. Adverse events
    b. Tolerability
        i. Achieving maximum dose
        ii. Achieving half maximum dose
        iii. Discontinuing medication (maximum dose of zero)
        iv. Maximum dose achieved
2. Analyses
    a. Total number of adverse events reported by body system (MedDRA SOC) will be tabulated by drug.
    b. Number and percentage of patients with each type of event by body system (MedDRA SOC) will be tabulated by drug.
    c. Total number of recorded adverse events will be reported by drug.

d. The percentage of patients who reported at least one adverse effect will be reported by drug.
e. For all tolerability measures except maximum dose, the percentage achieving the endpoint will be tabulated.
f. For maximum dose achieved, the average and range will be calculated for each drug. Also, 95% confidence intervals will be calculated for each drug. This will be achieved by treating maximum dose as the outcome in a mixed model analysis (similar to the primary outcome analysis) with a single predictor of drug and with patient as a random effect. Least squares means and their 95% confidence intervals will be calculated.