TRADITIONAL VERSUS EARLY AGGRESSIVE THERAPY FOR MULTIPLE SCLEROSIS (TREAT-MS) TRIAL

Protocol Number: IRB00143534

National Clinical Trial (NCT) Identified Number: NCT03500328

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Sponsor: Johns Hopkins University School of Medicine

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
4.1, 4.3	Added ofatumumab (Kesimpta) to the list of higher-efficacy medications after SAC vote and FDA approval (Tables 4 and 5). Added generic dimethyl fumarate as a traditional therapy after SAC vote and FDA approval.	Ofatumumab (Kesimpta) and generic dimethyl fumarate have been approved by the FDA and are available as treatment options for enrolled patients.
5.2	Prior exposure to ofatumumab will exclude potential candidates from participation in this study.	Similar to other B-cell therapies, any treatment with ofatumumab in the past is an exclusion criterion.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the Patient-Centered Outcomes Research Institute (PCORI) Terms and Conditions of Award. The Principal Investigator (PI) at each participating site will assure that no deviation from, or changes to, the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**TR**aditional versus **E**arly **A**ggressive **T**herapy for **M**ultiple **S**clerosis (**TREAT-MS**) Trial
Study Description:	The **TR**aditional versus **E**arly **A**ggressive **T**herapy for **Multiple Sclerosis** (**TREAT-MS**) trial is a pragmatic, randomized controlled trial that has two primary aims: 1) to evaluate, jointly and independently among patients with multiple sclerosis (MS) deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among MS patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability.
Objectives:	Primary Objective: To evaluate, independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a first-line therapy, influences the intermediate-term risk of disability accumulation. Secondary Objective: To evaluate if, among patients deemed at lower risk for disability accumulation who start on first-line MS therapies but

experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability accumulation.

Endpoints:

Primary Endpoint:
The primary endpoint is **time to sustained disability progression**, as measured by the **Expanded Disability Status Scale plus (EDSS+):** a composite endpoint that includes EDSS change (change at any 6 month time point of $\geq$ 1.0 point if baseline EDSS $\leq$ 5.5 or of $\geq$ 0.5 if baseline EDSS $\geq$ 6.0, that is sustained 6 months later) **OR** 20% worsening on **either** of two specific components of the Multiple Sclerosis Functional Composite (MSFC), the timed 25-foot walk test (T25FWT) and the nine hole peg test (9HPT) that is sustained 6 months later.

Secondary Endpoints:
Patient-Determined Disease Steps (PDDS): This patient-reported outcome (PRO) is a self-assessment scale of MS disease status.
MSFC: The original MSFC consists of the Paced Auditory Serial Addition Test (PASAT), the 9HPT, and the T25FWT; low-contrast letter acuity (binocular, 2.5% contrast Sloan charts) will also be included and both composite MSFC and individual scores will be evaluated.
Relapse recovery: Among participants identified to have a relapse, relapse recovery will be defined as complete or incomplete based on a) patient self-report, and 2) neurologic examination (those who have increased Functional System scores, corresponding to the relapse symptoms, of 1.0 point or greater for at least 6 months after the relapse onset, without subsequent accrual of worsening in that same Functional System (e.g. more indicative of progression), will be considered to have incomplete relapse recovery).
Cognition using Symbol Digit Modalities Test (SDMT): The SDMT is commonly used in MS to assess processing speed and will be administered orally and used to evaluate changes in cognition throughout the study.
Multiple Sclerosis Impact Scale (MSIS-29): The MSIS-29 will be used to evaluate the impact of MS on the participants.
Quality of Life in Neurological Disorders (Neuro-QoL): The Neuro-QoL will be administered as an electronic PRO to capture health-related quality of life. Neuro-QoL includes subscales that capture depression and fatigue.
Social status: The incidence of change in employment to "disabled" or "looking for work, unemployed," using the NINDS MS Common Data Elements template, will be evaluated in all participants as an electronic PRO. Incident divorce or separation, among those who previously were married or in a domestic partnership, will likewise be captured.
Serious Adverse Events (SAEs): Serious adverse events (clinically significant infections, malignancies, or the development of other serious

comorbidities, as well as unplanned hospitalizations [for non-elective issues excluding hospitalizations for MS relapse] and death), or other adverse events meaningful enough to lead to medication discontinuation will be noted in the progress note and collected as a secondary outcome.

Tertiary Endpoints:

Brain MRI evidence of neurodegeneration: Changes in brain MRI measures of neurodegeneration, including whole brain and normalized gray matter volumes as well as newer metrics such as cortical thickness and subcortical gray matter compartment volumes, and measures of T2 lesion burden, will be assessed.

Relapses: The number of relapses (new or worsening neurologic symptoms lasting for 24 hours or more in the absence of fever) will be assessed.

New brain lesions: The number of new/enlarging T2-weighted hyperintense lesions and T1-weighted hypointense lesions will be quantified on each scan.

Optical coherence tomography (OCT): Retinal nerve fiber layer and ganglion cell/inner plexiform thickness will be evaluated among patients at centers with access to OCT as standard of care.

Number of new medications, escalated dosage of medications, and non-pharmacologic interventions for MS-related symptoms: As an exploratory outcome, the number of newly-prescribed or dose-escalated medications used for treating MS symptoms (including pain, weakness, numbness/tingling, trouble walking, cognitive problems, fatigue, depression, anxiety, visual dysfunction, spasticity, vertigo, or bladder/bowel/sexual dysfunction) during the trial will be evaluated using the electronic health record. The final list of medications that will be considered as symptomatic therapies was approved by the SAC, and includes the list of medications found in the Appendix. In addition, non-pharmacologic interventions (and referrals to other healthcare providers) for symptom management will also be captured.

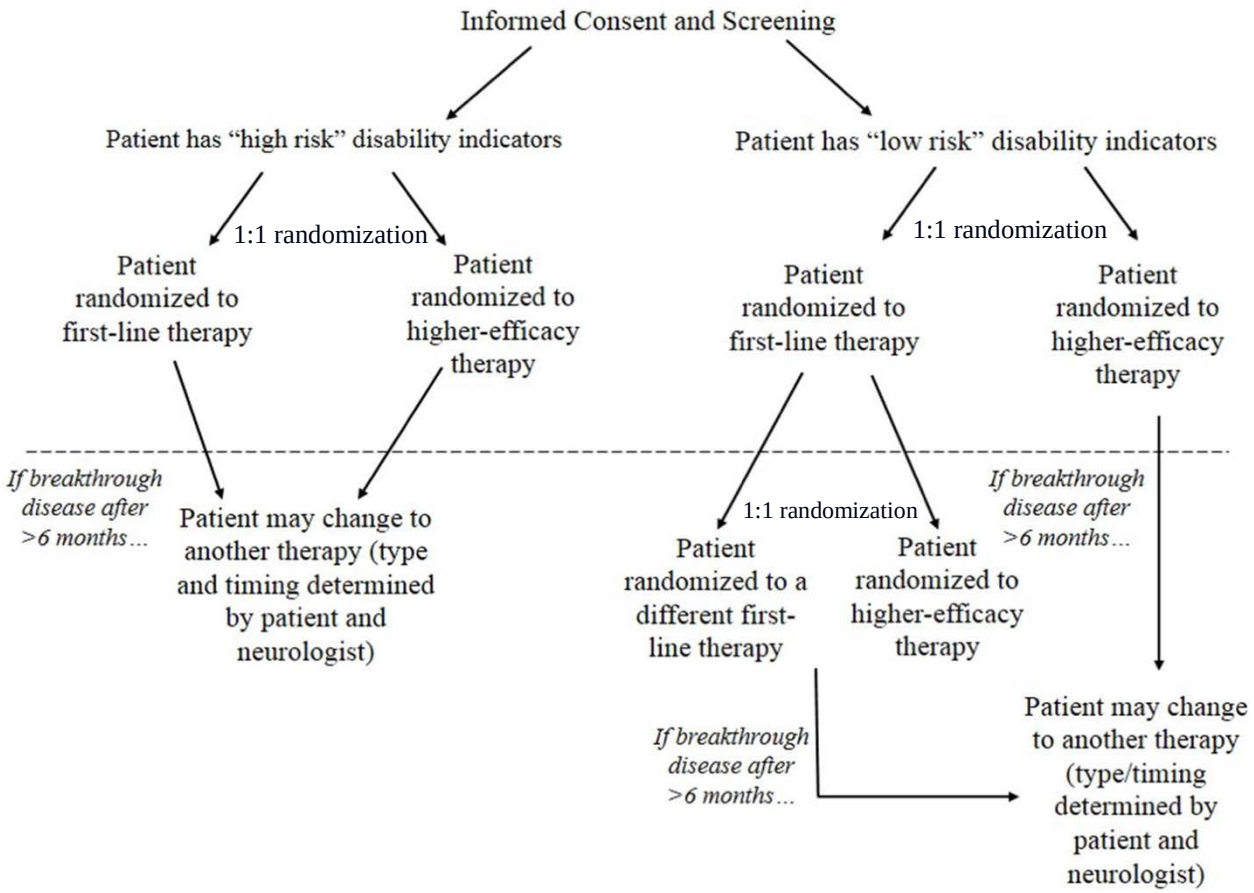
Study Population: This study will be conducted in male or female patients aged 18 to 60 years, inclusive, with a diagnosis of relapsing-remitting multiple sclerosis (RRMS) by the 2017 McDonald criteria. A total of 900 patients will be enrolled in the study.

Detailed criteria are described in the protocol.

Phase: N/A

Description of Sites/Facilities Enrolling Participants:	Approximately 45 sites across the United States, representing academic medical centers and private neurology practices with specialists in multiple sclerosis
Description of Study Intervention:	Participants will be stratified by whether they are at higher versus lower risk for long-term disability and then randomized 1:1 to a higher-efficacy versus a traditional, first-line disease-modifying therapy (DMT) class. With their treating neurologist (a member of the study team), participants will choose the specific therapy within the therapy class that is most appropriate for them.
Study Duration:	Study duration is approximately 67 months.
Participant Duration:	Study participation will range from 27 – 63 months, depending on enrollment date.

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1. Visit Schedule and Activities

Visit Activity	Screening/ Baseline	Month 6 +/- 3 months	Month 12 +/- 3 months	Month 18 +/- 3 months	Month 24 +/- 3 months	Month 30 +/- 3 months	Month 36 +/- 3 months	Month 42 +/- 3 months	Month 48 +/- 3 months	Month 54 +/- 3 months	Month 60 +/- 3 months
Informed consent, screening/baseline evaluation	X										
Medical history, relapse assessment and MRI review	X	X	X	X	X	X	X	X	X	X	X
Risk Stratification	X										
Randomization	X										
Medication review	X	X	X	X	X	X	X	X	X	X	X
Blinded EDSS exam	X	X	X	X	X	X	X	X	X	X	X
MS Functional Composite (MSFC)-4 (with low-contrast visual acuity)	X	X**	X	X**	X	X**	X	X**	X	X**	X
Symbol Digit Modalities Test	X		X		X				X	X	X
Patient-Determined Disease Steps		X	X		X		X		X	X	X
Brain MRI*	X	X	X		X		X		X		X
OCT (if standard of care)	X		X		X		X		X		X
Safety/ Adverse event assessment		X	X	X	X	X	X	X	X	X	X

*The baseline MRI will be done per local standard of care (some sites may choose not to do it for patients who have recently had imaging; since the "month 6" MRI will be used for comparative baseline for both analyses and clinical decision-making, repeat MRI at time of enrollment is up to discretion of treating physicians). ** Timed 25-foot walk test and nine hole peg test only.

Table 2. Home based electronic Patient-Reported Outcome (ePRO) Schedule

Home-based ePRO	Baseline	Month 3 +/- 3 months	Month 9 +/- 3 months	Month 21 +/- 3 months	Month 33 +/- 3 months	Month 45 +/- 3 months	Month 48 +/- 3 months	Month 60/ End of Trial
MSIS-29*	X	X	X	X	X	X	X	X
Patient-Determined Disease Steps	X	X	X	X	X	X	X	X
Neuro-QoL**	X	X	X	X	X	X	X	X
Medication adherence survey		X	X	X	X	X	X	X
Social status (including employment status) and lifestyle factors (diet and exercise)	X		X		X		X	X

* MSIS-29: Multiple Sclerosis Impact Scale; ** Neuro-QoL: Quality of Life in Neurological Disorders

2 INTRODUCTION

2.1 STUDY RATIONALE

FDA-approved multiple sclerosis (MS) disease-modifying therapies (DMTs) target the relapsing phase of MS but have minimal impact once the progressive phase has begun. It is unclear if, in the relapsing phase, there is an advantage of early aggressive therapy with respect to preventing long-term disability. The infectious risks and other complications associated with higher-efficacy treatments highlight the need to quantify their effectiveness in preventing disability.

The **TR**aditional versus **E**arly **A**ggressive **T**herapy for **MS** (**TREAT-MS)** trial is a pragmatic, randomized controlled trial that has two primary aims: 1) to evaluate, jointly and independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability.

Hypotheses/Objectives: The main hypothesis is that intermediate-term disability will be reduced by earlier use of higher-efficacy medications. Additional objectives include a) evaluating the magnitude of the treatment effect in patients deemed to be at higher risk versus lower risk of longer-term disability (we hypothesize that the effect size will be greater in the former group) and b) evaluating if, among those without indications of a high risk of longer-term disability, breakthrough disease can be successfully managed by switching to a different first-line therapy or if escalation is required at that time (we hypothesize that switching to a higher-efficacy therapy will be more effective in preventing disability in this group).

There is a great unmet need to identify the most appropriate treatment strategy for people with MS, especially early in the disease course when it may be possible to maximize an individual's chance for preventing long-term disability. There is a paucity of evidence-based guidelines to help clinicians, patients, and payers determine which treatment strategy is best for an individual with MS. Making treatment decisions is a daunting task, and the individualized benefit-risk assessment becomes increasingly difficult as new therapies emerge. Without the availability of direct comparative trials, clinicians and patients are forced to scrutinize observational studies that only provide basic insights into what may be the best treatment path moving forward. It is equally challenging to define what constitutes a suboptimal response to a DMT for an individual patient. Clinicians lack guidance on when to switch therapies and whether to consider a different first-line or if they should escalate immediately to higher-efficacy therapies, so further consensus is needed to determine the optimal time to switch therapies and escalate therapy if an individual is on a first-line therapy from the start. The **TREAT-MS** trial will help inform patients and the broader health care community on whether patients would most benefit from early, possibly more risky aggressive therapy or if starting with a less aggressive

(and, often, less risky) therapy, followed by a switch if breakthrough disease occurs, is warranted. In addition, this study may help identify specific patient populations and/or short-term clinical and paraclinical *biomarkers that are strongly predictive of long-term disability that can ensue from MS.*

Accrual of sustained disability is the most feared complication for people with MS, and the patient's own perception of their well-being or ill-being has a profound impact on their quality of life. The heterogeneity and unpredictability of MS, along with lack of agreed upon treatment guidelines, augments this fear, leading to a significant negative impact on quality of life. Even patients who are deemed to have "mild" MS experience a significant negative impact on their health-related quality of life that is similar in magnitude to what patients with other severe chronic conditions (i.e., congestive heart failure and chronic obstructive pulmonary disease) report.[1] An extremely important goal for any intervention is to help improve or maintain a high quality of life; therefore, in addition to classic clinical endpoints (e.g. slowing disability progression), obtaining PROs in MS trials is integral to better understanding the full impact of a treatment. An individual's perceptions of how they are doing is of utmost importance; therefore, the **TREAT-MS** trial will capture several important and meaningful PROs that will shed light on what treatment strategies may be the best from a patient-centered perspective.

Rationale for biorepository: Biomarkers predictive of a) long-term disability in MS and b) responses to disease-modifying therapy (whether a broad therapy response or a response to a specific therapy-) are sorely needed for people with MS. While new data suggest that higher neurofilament light chain (NfL) levels may portend a worse long-term prognosis for MS, the interpretation of the results may be limited by the fact that the data were generated from either observational, non-randomized cohorts or from clinical trials in which patients who were chosen on the basis of a certain degree of recent disease activity were included. Hence, there is a great unmet need to evaluate such novel biomarkers in a prospective, less biased study in order to assess its true clinical applicability and generalizability. The TREAT-MS trial, given its pragmatic design and broad inclusion criteria, the inclusion of essentially newly-diagnosed, treatment-naïve patients, as well as its goals of sustained follow-up, represents an incredible opportunity in which to collect biospecimens for subsequent use for biomarker discovery. The biobanking substudy will be optional; each site PI will determine if their site will participate in the substudy.

2.2 BACKGROUND

Background on Multiple Sclerosis

MS, a top cause of neurologic disability, affects at least 400,000 people in the United States alone, and its incidence has increased in the past 50 years; in fact, unpublished data recently showed that nearly 1 million people are now estimated to be living with MS in the United States.[2] At onset, most people with MS have episodic "relapses" of neurologic dysfunction. While some do not recover completely from relapses and thus acquire lasting disability in a step-wise fashion, it is when patients with relapsing-remitting MS transition to secondary

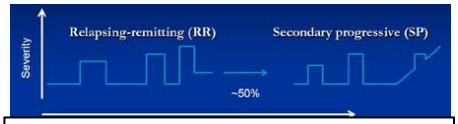


Figure 1. Relapsing-remitting vs. secondary progressive (SP) MS. While SPMS patients may still have relapses, the phase is characterized by a progressive decline in neurologic function.

progressive MS, which occurs in a sizable proportion, that there is slow accrual of disability, with or without relapses (see Figure 1).[3]
Relapses are caused by demyelinating autoimmune attacks, while secondary progression is likely due to the steady accumulation of neurodegeneration, which does not seem to respond well to MS therapies.[4,5] As such, FDA-approved DMTs for MS, which modulate and help prevent the autoimmune attacks, target the relapsing phase of the disease but have minimal impact on slow disability accrual once the progressive phase has begun. ***Whether long-term disability can be prevented, in particular by higher-efficacy and traditional, first-line therapies alike, is unclear***. In shorter-term trials, a recent systematic review/meta-analysis showed that "***clear reductions in [relapse rate] are accompanied by more uncertain changes in disability progression***," noting further that while relapses do affect patient well-being, "it is the accumulation of disability which has the greatest long-term clinical, social, and economic impact on patients and society."[6] The authors also caution that making inferences about the longer-term effect of therapies during short trials "may be limited." Data about the impact of MS therapies on long-term disability risk are conflicting. ***The infectious risks and other complications associated with higher-efficacy treatments further highlight the need for evaluating their relative effectiveness in disability prevention.*** For example, revised estimates for natalizumab-associated progressive multifocal leukoencephalopathy in JC virus-positive patients treated for >24 months may be as high as one in forty-four patients.[7] **There is an unmet need to identify if specific treatment strategies during the relapsing-remitting phase of MS can prevent, delay, or reduce intermediate- to longer-term disability accrual,** particularly as some approaches may require patients to accept serious risks.

Specific Aims and Trial Overview

Aim 1. To evaluate, independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a first-line therapy, influences the intermediate-term risk of disability accumulation or change in patient-reported, MS-related outcomes.

Aim 2. To evaluate if, among patients deemed at lower risk for disability accumulation who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability accumulation or patient-reported, MS-related outcomes.

In this pragmatic, randomized controlled trial, patients will be randomized, stratified by disability risk, to higher-efficacy versus first-line therapies; those at low risk of disability who are randomized to a first-line therapy and who experience breakthrough disease will be re-randomized to higher-efficacy therapy or to a different first-line therapy. The trial is designed to evaluate initial therapeutic strategies and to evaluate strategies for switching therapies with respect to outcomes that are meaningful to people with MS, including disability but also PROs such as fatigue, cognition, and other meaningful outcomes often impacted by MS.

Current Therapies for Multiple Sclerosis
There are now multiple effective FDA-approved therapies for relapsing-remitting MS.[8] These therapies can often be optimized to achieve good suppression of the inflammatory aspects of MS

(relapses and new lesions on brain magnetic resonance imaging (MRI)), especially earlier in the course when the inflammatory activity seems to be most robust. However, not all patients respond optimally to the first MS DMTs.[9] Traditionally, when limited options were available, clinicians would typically start MS patients on an injectable (first-line/lower potency) therapy, and if there was ongoing activity despite treatment, they would recommend switching to another injectable therapy in hopes it would keep the disease at bay. Even when the first selective, higher-efficacy therapy (natalizumab) came to market, clinicians would often start treatment with an injectable therapy, escalating only when one (or, often, even more than one) first-line agent failed. This treatment escalation approach is still the standard practice for many clinicians, even with the expanding landscape of MS therapeutics, in part due to the long-term track record of safety of these medications. However, with the advent of more higher-efficacy immune therapies in the past several years, *the question arises as to whether a more aggressive treatment approach up front may be warranted and, if so, in which patient subgroups*. A recent study to assess practice patterns of MS experts in the United States showed that many clinicians are now adopting a more aggressive early treatment approach, but this was not unanimous and is only based on consensus opinions.[10] ***The appropriate strategies for treating MS remain to be identified***, particularly regarding the order and timing of DMT use.

Pivotal clinical trials for approved MS disease-modifying therapies have shown no to modest differences in the accrual of disability during the trial period. However, such trials typically last for only two years, and any disability benefit in such a time period is likely due to the fact that relapses themselves are reduced in frequency or that the medications improve recovery from relapses that do occur (and, by extension, there is less residual disability) rather than to reductions in slowly-accumulating neurodegeneration.[11] To complicate the picture further, the higher-efficacy therapies are associated with a greater risk of serious adverse events, and one meta-analysis of trial data suggested similar effects of "first-line" and "second-line" disease-modifying therapies on disability progression during the trial period,[12] suggesting there is equipoise between the intervention arms and comparator arms chosen for the proposed trial.

Whether a more aggressive treatment strategy early in MS prevents longer-term disability is thus unknown. Inflammatory MS activity, especially in the first year or two after symptom onset, is considered an indicator of poor prognosis for the long term,[13] suggesting that early initiation of aggressive therapies may prevent such activity and thus mitigate disability years later. Early inflammatory events are associated with increased disability over time, especially if there is breakthrough while on first-line MS therapy.[14] It is not known, however, if these and other prognostic indicators aren't simply harbingers of a worse outcome that can't be modified by even very aggressive therapies. Observational studies regarding the impact of MS therapies on long-term disability provide conflicting reports. One study suggested that interferon beta did not meaningfully change the time to requiring a cane to walk (Expanded Disability Status Scale [EDSS] 6.0) compared to no treatment;[15] another reported that moderately-disabled MS patients who were started on natalizumab (higher-efficacy), saw reductions in short-term, but not later (4 to 7 years), disability.[16] On the other hand, there may have been bias at play (e.g. those destined for longer-term disability were more likely to be treated). A recent publication showed that the age at which MS patients reached a disability level of EDSS 6.0 is much older now compared to the time when there were limited treatments options available.[17] A meta-analysis of 14 observational studies evaluating the impact of injectable (first-line) medications on long-term disability suggested that these therapies were associated with a lower risk

of MS progression over time.[18] Five-year follow-up data from the pivotal trials of the high-efficacy therapy alemtuzumab did show less disability progression in the alemtuzumab-treated patients, although it appears all of this benefit was in the early treatment phase, as there was no difference in the last 2 years of follow-up between groups.[19]

There is, thus, **a critical gap in evidence regarding whether, to prevent intermediate- and long-term disability, 1) an aggressive approach is warranted from the time of diagnosis, or 2) early escalation after lack of adequate response to first-line therapy is equally appropriate, particularly in people at lower risk of long-term disability**. While sophisticated observational studies may help to fill that gap to some extent, ideally a pragmatic, randomized trial that approaches this gap from the perspective of everyday clinical practice is needed in order to evaluate, in the most bias-free manner possible, the impact of the various treatment strategies. The proposed trial will address this gap, providing the evidence that patients and their clinicians need to evaluate their medication choices more carefully, particularly so they can judge if the non-trivial risk of infectious and other complications of higher-efficacy treatments is worth taking due to a greater potential to slow disease progression. ***This dilemma highlights the critical need for identifying ideal treatment approaches for persons with MS***.

Literature Relevant to the Intervention and Outcomes

Preliminary data, detailed below, demonstrate that: 1) in terms of reducing relapse risk, there is evidence to support switching to a different first- line therapy as well as to higher-efficacy therapies after breakthrough disease on a first-line agent, 2) there are several demographic or clinical predictors of disease activity in people with relapsing MS that may help divide patients into risk strata for randomization purposes, 3) disease-modifying therapies differentially impact optical coherence tomography (OCT) metrics of neurodegeneration, and 4) these same metrics predict long-term disability in people with MS.

Switching a patient with MS with breakthrough disease to another therapy (first-line as well as a second-line) is associated with reduced relapse risk. Prior sequential studies showed that switching therapies after breakthrough on the initial treatment is effective in reducing relapse risk. Among 597 MS patients started on an injectable (first-line) therapy, 101 switched to a different first-line therapy due to breakthrough disease activity.[20] Annualized relapse rate before and during the first treatment as well as after switch to another first-line therapy (after at least 24 months on therapy) was as follows:

Switching from interferon beta to glatiramer acetate: 0.50, 0.55, and 0.25

Switching from glatiramer acetate to interferon beta: 0.90, 0.50, and 0

Switching from one interferon beta to another interferon: 0.50, 0.68, and 0

In the second study, switching from a first-line to a second-line therapy, in a follow-up study, was also beneficial in terms of impact on the disease course.[21] Among 993 patients evaluated, 82 patients changed their treatment to a second-line medication (natalizumab or immunosuppressant therapy) due to breakthrough disease activity.

Switching from first-line therapy to natalizumab: 70% reduction in relapse rate (95% CI 50, 82%; p<0.001)

Switching from first-line therapy to immunosuppressant: 77% reduction in relapse rate (95% CI 59, 87%; p<0.001)

Large, observational studies have demonstrated a robust positive impact on MS disease activity after switching from first-line therapies to second-line therapies.[22-24] One demonstrated, using propensity scores, that transitioning to natalizumab was more effective than fingolimod for all outcomes except that there was no difference in the rate of sustained disability progression between the two groups.[24] Another study (n=366 per group) demonstrated that first-line natalizumab treatment was associated with a greater, sustained reduction in relapse rate, including in the higher disease activity subgroups, than injectable therapies.[25] Again, there was no difference in disability progression between the groups. While it appears that these therapies more effectively reduce relapses in the real-world setting (although some of the effect may relate to regression to the mean), the data do suggest, at the individual level, that *there is still equipoise in considering next steps in treatment when a first-line therapy fails*, particularly given the risks associated with the higher-efficacy therapies and their unclear benefit for long-term disability. These results also support the plan in the proposed trial that MS patients in the trial at low risk of disability progression, who are randomized to the first-line arm and experience breakthrough disease on that therapy, will be re-randomized to a different first-line therapy or to escalation to second-line therapy.

Several predictors of disease activity in early MS can be used to stratify patients into high-risk versus low-risk for disease activity for purposes of this trial. The literature cited below informed the Study Advisory Committee's (SAC's) decisions regarding how to define risk strata for the proposed trial.

Demographic characteristics may inform relapse frequency. Three hundred and thirty patients who were seen within the first year of disease onset were analyzed to determine predictors of having a second MS relapse within the first year of onset.[26] Younger age and non-white race (largely composed of African Americans) were identified as strong predictors thereof. These results are relevant since African Americans appear to be at higher risk of long-term disability over time, and some studies suggest an earlier age at diagnosis is associated with an earlier age of disability.[27,28]

Table 3. Predictors of Worse Second Event Recovery

Predictors of Worse Second Event Recovery			
Predictor	OR	95% CI	*p*
Age (per 10 years greater)	**1.40**	0.99, 1.97	0.058
Moderate second event	**5.44**	2.35, 12.59	<0.0001
Severe second event	**9.21**	2.99, 28.40	0.0001
Fair prior event recovery	**1.20**	**0.54, 2.69**	**0.66**
Poor prior event recovery	**4.94**	**1.70, 14.35**	**0.003**

Features of the MS presentation itself may be predictive of worse outcomes. Worse recovery from the first MS attack is strongly associated with increased odds of incomplete recovery from subsequent attacks (see Table 3 above),[29] which is relevant since poor recovery from early relapses predicts long-term disability; thus, early event recovery may be a factor for the SAC to consider in creating risk strata.[30] Since an infratentorial location of the first neurological attack is associated with earlier disability accumulation and because we have shown that anatomic location of the first attack is

associated with increased odds of that location being involved in further relapses, early relapse location was also considered in creating the risk strata.[31,32]

Disease-modifying therapies may differentially impact neurodegenerative measures that are linked to long-term disability. The Johns Hopkins MS Center OCT Research group has found that **the** type of MS therapy is longitudinally associated with differing declines in ganglion cell/inner plexiform (GCIP) layer thickness, a measurement obtained by non-invasive retinal imaging (OCT).[33] Poorly controlled inflammatory MS activity (e.g. relapses, new or active MRI lesions) was also shown to be associated with a faster decline in retinal integrity on OCT.[34] Furthermore, a novel OCT phenotype (increased inner nuclear layer thickness) predicts clinical and radiologic disease progression in MS.[35] In addition, either a single OCT scan or longitudinal scans demonstrating greater retinal damage are predictive of greater disability ten years later.[36]

Additional findings from this group demonstrate that cumulative retinal damage, as measured by OCT, corresponds with a decline in gray matter volume in the brain,[37] which is an established predictor of long-term disability in MS.[38,39] Based on these recent findings, OCT has become part of the standard of care, along with routine brain MRI, in monitoring the disease state of MS patients at the Johns Hopkins MS Center, supporting its use as a standard of care outcome measure in this trial where it is available. In totality, these observational studies demonstrate strong plausibility that higher-efficacy MS therapies will have a greater impact on longer-term disability than first-line therapies.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Group-level data from randomized trials have previously shown that higher-efficacy medications suppress relapses and new MRI lesions more than some first-line medications (not all have been compared head-to-head), but the differential risk of new disease activity at the individual level is less clear (i.e. several patients started on first-line medications effectively have no or negligible relapse/MRI activity). Regardless, any such disease activity after the time at which the medications are expected to be reasonably effective (e.g. six months) allows for the transition to a different therapy in the TREAT-MS trial, similar to or more lenient than the standard of care in many practices. Further, there is equipoise regarding the treatment assignment with respect to long-term disability, and the medications that will be used are already [or will be] available to treat MS. The only other substantive potential risk associated with trial participation per se is a risk to confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

There is no direct benefit anticipated for the patients enrolled in this study. The study has important potential benefits to MS patients in the future, however, as the results will provide critical information about whether early, aggressive therapy is warranted in all patients or just those with high-risk indicators for disability and will evaluate if, among those started on less potent therapies, early switch at the first sign of disease activity is an acceptable alternative to starting with an aggressive therapy.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Several mechanisms will help prevent loss of privacy. First, the VISION™ electronic data collection (EDC) system that will be used for the study is an FDA- and HIPAA-compliant platform (Prelude Dynamics Inc., Austin, Texas, www.PreludeDynamics.com; see section 10.1.9 Data Handling and Recordkeeping for additional details). Access to the data will be limited to study personnel and the database will be password-protected. Furthermore, each member of the study team will be limited to only the data they need to perform their tasks so that privacy is protected as much as possible. All patients will be assigned a unique study number, which will be used on all study documents so as to further protect privacy. Only study personnel who need to access the database will be given such access. Access by study coordinators will be restricted such that each coordinator can only see the study charts of patients enrolled at his or her center.

Those assigned to a traditional, first-line medication may be at increased risk for relapses/MRI activity compared to those assigned to a higher-efficacy medication, however, it is still well within the standard of care practice to start with a first-line medication (especially given the safety profile of some of these therapies) and switch therapies (either to another first-line therapy or to second-line) only when disease activity occurs. Thus, the associated risk of breakthrough disease is similar to what a patient in the real world, standard of care setting would face.

Those assigned to a higher-efficacy medication may be at risk for side effects of these medications that they may not have been exposed to outside the study had they chosen some of the first-line medications. The informed consent process will include a discussion of the risk of randomization. Choice of therapy within the assigned therapy class remains a participant/provider decision after they consider the efficacy data, side effects, ease of administration, and/or other factors.

The risks associated with the study are minimal, and an adequate protection plan is in place; as such, the potential benefits far exceed the potential risks. The participation of patients is completely voluntary; the alternative to the patients is to not participate in the study. Lack of participation will in no way compromise the relationship they have with their neurologists or the ongoing care they receive for their MS.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate, independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a first-line therapy, influences the	The primary endpoint is **time to sustained disability progression**, as measured by the **Expanded Disability Status Scale plus (EDSS+):** a composite endpoint that includes EDSS change (change at any 6 month time point of $\geq$ 1.0 point if baseline	EDSS+ was chosen as the primary endpoint because a) it is a clinical disability metric and the actual experience of worsened disability

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
intermediate-term risk of disability accumulation. To evaluate if, among patients deemed at lower risk for disability accumulation who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability accumulation.	EDSS is $\leq$ 5.5 or of $\geq$ 0.5 if baseline EDSS is $\geq$ 6.0, that is sustained 6 months later) **OR** 20% worsening on **either** of two specific components of the Multiple Sclerosis Functional Composite (MSFC), the timed 25-foot walk test (T25FWT) and the nine hole peg test (9HPT) that is sustained 6 months later.[40-45]	that is most meaningful to/feared by patients,[46] and b) the combination EDSS+ increases the sensitivity of detecting disability change over time[44]
Secondary		
To evaluate, independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a first-line therapy, influences change in patient-reported, MS-related outcomes. To evaluate if, among patients deemed at lower risk for disability accumulation who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different patient-reported, MS-related outcomes.	**Patient-Determined Disease Steps (PDDS):** This patient-reported outcome (PRO) is a self-assessment scale of MS disease status.[47] **MSFC:** The original MSFC consists of the Paced Auditory Serial Addition Test (PASAT), the 9-hole peg test, and the timed 25-foot walk test;[43] low-contrast letter acuity (binocular, 2.5% contrast Sloan charts)[48,49] will also be included and both composite MSFC and individual scores will be evaluated. **Relapse recovery:** Among participants identified to have a relapse, relapse recovery will be defined as complete or incomplete based on a) patient self-report, and 2) neurologic examination (those who have increased Functional System scores, corresponding to the relapse symptoms, of 1.0 point or greater for at least 6 months after the relapse onset, without subsequent accrual of worsening in that same Functional System (e.g. more indicative of progression), will	Secondary endpoints were chosen to reflect other meaningful measures of clinical disability (to corroborate the findings of the primary endpoint) as well as to capture a differential impact of treatment class on patient's well-being, as assessed by changes in health-related quality of life and social status. Further, substantial adverse events are important to patients as they weigh the risks and benefits of these therapeutic strategies.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	be considered to have incomplete relapse recovery).[3] **Cognition using Symbol Digit Modalities Test (SDMT):** The SDMT is commonly used in MS to assess processing speed and will be administered orally and used to evaluate changes in cognition throughout the study.[50-54] **Multiple Sclerosis Impact Scale (MSIS-29):** The MSIS-29 will be used to evaluate the impact of MS on the participants.[55] **Quality of Life in Neurological Disorders (Neuro-QoL):** The Neuro-QoL will be administered as an electronic PRO to capture health-related quality of life. Neuro-QoL includes subscales that capture depression and fatigue.[56-57] **Social status:** The incidence of change in employment to "disabled" or "looking for work, unemployed," using the NINDS MS Common Data Elements template, will be evaluated in all participants as an electronic PRO. Incident divorce or separation, among those who previously were married or in a domestic partnership, will likewise be captured.[57] **Serious Adverse Events (SAEs):** Serious adverse events (clinically significant infections, malignancies, or the development of other serious comorbidities, as well as unplanned hospitalizations [for non-elective issues, excluding MS relapse] and death), or other adverse events meaningful enough to lead to medication discontinuation will be noted in the progress note and collected as a secondary outcome.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
Tertiary objectives focus on measures that may be prognostic of longer-term disability or provide information on whether an early aggressive treatment approach is beneficial.	**Brain MRI evidence of neurodegeneration:** Changes in brain MRI measures of neurodegeneration, including whole brain and normalized gray matter volumes as well as newer metrics such as cortical thickness and subcortical gray matter compartment volumes, and measures of T2 lesion burden, will be assessed.[58-65] **Relapses:** The number of relapses (new or worsening neurologic symptoms lasting for 24 hours or more in the absence of fever) will be assessed. **New brain lesions:** The number of new/enlarging T2-weighted hyperintense lesions and T1-weighted hypointense lesions will be quantified on each scan. **Optical coherence tomography:** Retinal nerve fiber layer and ganglion cell/inner plexiform thickness will be evaluated among patients at centers and offices with access to OCT as standard of care.[66-70] **Number of new medications, escalated dosage of medications, and non-pharmacologic interventions for MS-related symptoms:** As an exploratory outcome, the number of newly-prescribed or dose-escalated medications used for treating MS symptoms (including pain, weakness, numbness/tingling, trouble walking, cognitive problems, fatigue, depression, anxiety, visual dysfunction, spasticity, vertigo, or bladder/bowel/sexual dysfunction)	Tertiary endpoints were those that were felt to be less patient-centered (e.g. MRI endpoints) but still very meaningful; for example, reductions in brain volumes, while not specifically patient-centered, are known to be prognostic of longer-term disability and thus, even if the trial doesn't meet the primary endpoint, a meaningful impact on brain volumes of the differential treatment strategy may still have even longer-term benefit. The other endpoints are those that are more exploratory but still may provide useful information about the relative benefit (or absence thereof) of a more aggressive early treatment approach.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	during the trial will be evaluated using the electronic health record. The final list of medications that will be considered as symptomatic therapies was approved by the SAC, and includes the list of medications found in the Appendix.[71-72] In addition, non-pharmacologic interventions (and referrals to other healthcare providers) for symptom management will also be captured.	
Biobanking Substudy		
Our overall goal is to identify biomarkers of long-term prognosis and treatment response in MS. An additional goal is to create a biorepository that can be leveraged for future studies.	Serum neurofilament light chain is the most promising candidate biomarker to date; however, storage of serum, DNA, and peripheral blood mononuclear cells will allow for a rich secondary dataset from which future biological studies can emerge.	The study and validation of prognostic biomarkers will allow for the identification of patients who may benefit the most in the future from a more aggressive treatment strategy up front, while identifying biomarkers of treatment response will allow for the future discrimination of whether or not a treatment is working prior to the development of neurologic symptoms that may be irreversible and permanent.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The **TR**aditional versus **E**arly **A**ggressive **T**herapy for **M**ultiple **S**clerosis (**TREAT-MS**) Trial is a pragmatic, randomized controlled trial of the impact of early, aggressive versus traditional disease-modifying therapies on intermediate-term rater-blinded disability in people with MS. The trial has two primary aims: 1) to evaluate, jointly and independently among patients with multiple sclerosis (MS) deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among MS patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability.

Newly diagnosed people with MS will be divided into two groups based on suspected risk for long term disability, as determined by a group of MS expert stakeholders; the Study Advisory Committee (SAC). The first group will include those with "high-risk" indicators for aggressive disease (see below for trial definition) versus low-risk patients. Within each group, eligible participants will be randomized 1:1, to "higher-efficacy" therapies versus first-line therapies (see Table 4 on page 19 for categorization of DMTs for the TREAT-MS trial). The final determinants of what constitutes high- versus low-risk, as well as first-line versus higher-efficacy therapy, was established by the SAC prior to the finalization of the protocol and is detailed below. Notably, not all factors associated with long-term disability were included in the definition, as it was felt that the factors used needed to be simple, practical and assessable by general neurologists in the future using information available to them in a standard of care setting.

Criteria for classifying participants as being at **high risk of longer-term disability** depend on duration since first attack at time of enrollment as detailed below:

1) **Enrollment within 6 months of 1st attack: high risk if both**
   a) Clinical or radiographic involvement of the spinal cord **OR** brainstem/cerebellum
      AND
   b) MRI with >10 T2 lesions* **OR** ≥4 Gadolinium-positive (Gad+) lesions,* **OR** another attack in the first 6 months since the 1st attack, **OR** new lesions on MRI if a subsequent MRI is available already

2) **Enrollment > 6 months since 1st attack: high risk if any 2 of the 4 are true**
   a) Clinical or radiographic involvement of the spinal cord **OR** brainstem/cerebellum
   b) MRI with >10 T2 lesions* **OR** ≥4 Gad+ lesions*
   c) Residual damage (incomplete recovery based on exam [Functional System Score ≥2, with the deficit(s) on exam corresponding to the region of prior relapse])**
   d) Ongoing disease activity in the past year: 2 or more relapses **OR** ≥3 new lesions on MRI in the past year **OR** ≥2 gad+ lesions

   * The >10 T2 lesions **OR** ≥4 Gad+ lesions only applies to the brain based on the manuscript by Brex and colleagues.[73] It is recommended for clinicians to only count the brain lesions that appear demyelinating in nature. Non-specific white matter lesions (i.e., subcortical lesions)

should not be counted unless the clinician feels they are demyelinating in appearance and secondary to MS.
** If the patient has had more than one relapse, the incomplete recovery should be attributable to an attack that began > 6 months ago.

Participants will then be randomized, 1:1 within strata, to a higher-efficacy versus first-line therapy as classified by the SAC for the TREAT-MS Trial (see Table 4 below). Also, the SAC agreed to automatically classify generics/biosimilars in the same group as the originally-approved medication. If concerns are raised about the automatic classification for a specific generic/biosimilar by an SAC member(s), they must be reported to the JHCC within 14 days of FDA approval. These concerns will then be reviewed by the entire SAC in order to determine if the automatic classification is appropriate for the specific generic/biosimilar in question. Final classification will be based on consensus voting.

Table 4. Classification of Disease-Modifying Therapies Currently Used in the Clinical Practice Setting for TREAT-MS Trial

First-line (Traditional) Therapies	Second-line (Higher-efficacy) Therapies
Glatiramer acetate (Copaxone, Glatopa, and other generics)	Natalizumab (Tysabri)
Intramuscular interferon (Avonex)	Alemtuzumab (Lemtrada)
Subcutaneous interferon (Betaseron, Extavia, Rebif)	Ocrelizumab (Ocrevus)
Pegylated interferon (Plegridy)	Rituximab (Rituxan)
Teriflunomide (Aubagio)	Cladribine (Mavenclad)
Dimethyl fumarate (Tecfidera and generics)	Ofatumumab (Kesimpta)
Diroximel fumarate (Vumerity)	
Fingolimod (Gilenya and generics)	
Siponimod (Mayzent)	
Ozanimod (Zeposia)	

With their neurologists (who will be members of the study team), participants will choose the therapy within the category that is most appropriate for them, based on efficacy data, risk factors for/concerns about adverse events, schedule, or other factors. The factors that supported each individual choice will be documented at baseline and at any point a treatment switch is made.

The main hypothesis is that intermediate-term disability will be reduced by earlier use of higher-efficacy medications. Additional objectives include: a) evaluating the magnitude of the treatment effect in patients deemed to be at higher risk versus lower risk of longer-term disability (we hypothesize that the effect size will be greater in the former group) and b) evaluating if, among those without indications of a high risk of longer-term disability, breakthrough disease can be successfully managed by switching to a different first-line therapy or if escalation is required at that time (we hypothesize that switching to a higher-efficacy therapy will be more effective in preventing disability in this group).

Neither treating physicians nor the participants will be blinded to the treatment they receive. However, the primary outcome is disability progression and to minimize bias, the EDSS examiner will be blinded to treatment, as will be the person administering the T25FWT and other elements of the MSFC, the

cognitive tasks, and the visual assessment. In addition, every effort will be made to prevent missing data so as to avoid associated bias and reductions in power.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This trial is designed to **maximize flexibility**, in line with a pragmatic trial as defined by Thorpe et al.[74] Even for the two portions of the trial that involve randomization, the "control" arm is not a placebo but is an active comparator. Further, there is wide latitude within an arm for each patient/physician team to make a decision among the available medications. Finally, great autonomy is given to the individual patient/physician team if the patient meets breakthrough disease criteria (the first time there is breakthrough if the person is considered at high risk of long-term disability or breaks through higher-efficacy therapies despite being considered at low risk for disability, or after the second episode of breakthrough in the subset of low-risk patients that were re-randomized to a second first-line therapy versus higher-efficacy therapy).

4.3 JUSTIFICATION FOR DOSE

Medication doses and safety monitoring will be per standard of care for all drugs listed in Table 4 on page 19 and any newly approved DMTs added during the trial. However, as is consistent with a pragmatic trial, we will not interfere with dosage reductions made by local providers/patients. For example, occasionally providers suggest reducing the frequency of taking one of the oral medications in order to avoid severe lymphopenia or side effects like gastrointestinal distress. The protocol will not interfere with the practice of the provider in this regard, as such modifications would be consistent with an effectiveness, pragmatic trial. However, dosage reductions will be documented in case report forms (CRFs) along with the reason(s) for dose reduction.

Providers should not utilize dosages of any of the medications that exceed the maximally approved dosage for MS (or, in the case of rituximab, the maximally approved dosage for rheumatoid arthritis). Approved maximum doses for the medications classified for use in this study are listed in Table 5 below.

Table 5. Maximum FDA approved dosage(s) for TREAT-MS Trial Therapies

First-line (Traditional) Therapies	**Maximum FDA-approved dosage(s) for MS***
Glatiramer acetate (Copaxone, Glatopa, and other generics)	20 mg SC daily, or 40 mg SC three times a week
Intramuscular interferon (Avonex)	30 mcg IM weekly
Subcutaneous interferon (Betaseron, Extavia, Rebif)	0.25 mg SC every other day (Betaseron, Extavia); 44 mcg SC three times a week (Rebif)
Pegylated interferon (Plegridy)	125 mcg SC every 14 days
Teriflunomide (Aubagio)	14 mg PO daily
Dimethyl fumarate (Tecfidera and generics)	240 mg PO twice a day
Diroximel fumarate (Vumerity)	462 mg PO twice a day
Fingolimod (Gilenya and generics)	0.5 mg PO daily
Siponimod (Mayzent)	1 mg PO daily* or 2 mg PO daily**

Ozanimod (Zeposia)	0.92 mg PO daily
Higher-efficacy Therapies	
Natalizumab (Tysabri)	300 mg IV every 4 weeks
Alemtuzumab (Lemtrada)	12 mg IV daily x 5 days; 1 year later: 12 mg IV daily x 3 days
Ocrelizumab (Ocrevus)	300 mg IV q 2 weeks (for 2 doses) at initiation; subsequently, 600 mg IV q 6 months
Rituximab (Rituxan)	1000 mg IV q 2 weeks (for 2 doses); may repeat q 16-24 weeks***
Cladribine (Mavenclad)	3.5 mg per kg body weight PO divided into 2 yearly treatment courses (1.75 mg per kg body weight each year); each yearly treatment course is divided into 2 treatment cycles; administer cycle dosage as 1 or 2 tablets once daily over 4-5 consecutive days
Ofatumumab (Kesimpta)	20 mg SC weekly for weeks 0, 1 and 2; 20 mg SC monthly starting at week 4

SC= subcutaneous; IM=intramuscular; PO=oral; IV=intravenous
* patients with CYP2C9 genotypes *1/*3 or *2/*3
** patients with CYP2C9 genotypes *1/*1, *1/*2 or *2/*2
***the maximum FDA-approved dosage for rituximab, chosen from the rheumatoid arthritis label (which is also the maximum dosage used in standard of care MS practice setting), is provided.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

In order to maximize the follow-up time on treatment and thus the opportunity to evaluate the true impact of the treatment strategies on intermediate-term disability, we will censor patients' follow-up data at month 67 of the study. This strategy will ensure that all participants receive a minimum of 2.25 years of follow-up; some will be followed for more than 5 years. Participants enrolled early in the trial may be asked for one more set of ePROs to be completed within 3 months after completion of the month 54 or month 60 visit. Participants enrolled toward the end of the enrollment period may complete only through the month 24 visit or the month 21 ePROs.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

The inclusion criteria and the rationale for each criterion are presented in Table 6 below. These criteria were developed to maximize the generalizability of the results.

Table 6. Inclusion Criteria and Rationale

Criterion	Rationale
Aged 18-60 years	Want results to be as generalizable as possible; many MS specialists would not initiate therapy above age 60
Meets 2017 McDonald criteria for relapsing-remitting MS (patients with clinically isolated syndrome [CIS] are not eligible)	All MS medications are approved for relapsing forms of MS
Must be *EITHER* JC virus antibody negative or low positive (index antibody titer <0.9), *OR* negative for: Hepatitis B* and C,* tuberculosis**	Subjects need to be safe to take ≥ 1 higher-efficacy therapy in order to be eligible for randomization to that arm of the study
HIV negative[#]	Would not likely use higher-efficacy therapies in the HIV-positive population in the real-world setting due to possible infectious risks
No chemotherapy in past year; if patient has prior history of chemotherapy or malignancy, documentation in chart explaining why potential risks of higher-efficacy therapy are justified	Categorical exclusion of all patients with history of malignancy or remote chemotherapy limits the generalizability of results; on the other hand, in clinical practice, may not consider higher-efficacy MS treatments in people at risk of cancer progression/recurrence

**patients who demonstrate satisfactory use of antivirals for Hepatitis B or who successfully completed treatment for Hepatitis C may be enrolled, at the discretion of the treating physician and with documentation of approval by a gastroenterologist; **Patients with past history of appropriately-treated TB (latent or active) are eligible*

[#]HIV screening is required per standard of care if it has not been done in the 12 months prior to screening for the study (recommended time frame by the Centers for Disease Control and Prevention).[75]

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior treatment with rituximab, ocrelizumab, ofatumumab, alemtuzumab, mitoxantrone or cladribine
2. Prior treatment with any other MS DMT for more than 6 months*

3. Prior treatment with experimental aggressive therapies (e.g., T-cell vaccine, total lymphoid radiation, stem cells)
4. Treatment with teriflunomide within past 2 years (even for ≤ 6 months), unless rapid wash out done (i.e., with cholestyramine or activated charcoal)
5. Treatment in the past 6 months with any MS DMT
6. Prior treatment with any other investigational immune-modulating /suppressing drug for MS not listed above
7. Pregnant or breast-feeding**
8. Women of child-bearing age who are planning or strongly considering conception during the study time frame

   * If prior treatment with any other MS DMT for ≤ 6 months, reason for discontinuation must not have been breakthrough disease

   ** Pregnancy testing is not routinely done per standard of care at Johns Hopkins prior to prescribing a new medication to treat MS and therefore is not required per protocol. Individual sites may routinely test for pregnancy per their standard of care prior to prescribing a new medication to treat MS, so testing is left to the discretion of the treating provider.

5.3 LIFESTYLE CONSIDERATIONS

Not applicable

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but do not subsequently randomly receive the study intervention or enter in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.[76,77] Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of pregnancy/breast-feeding or exposure to a first-line MS DMT within 6 months of screening may be rescreened at a later date as appropriate. Rescreened participants should be assigned the same participant number as for their initial screening.

If safety tests are not completed yet and the person is determined ineligible (screen failure) based on the results of tests ordered at the baseline/randomization visit, the randomization will be returned to the pool for reassignment. Likewise, if a participant is unable to obtain insurance authorization for a medication within the therapy class s/he has been randomized to or if a participant is enrolled in error based on inclusion/exclusion criteria (e.g., site learns after completing the baseline visit that the patient had received an MS disease-modifying therapy in the 6 months preceding enrollment), the participant will be deemed a screen failure and the randomization slot returned to the pool for reassignment.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Approximately 45 sites in the United States will recruit and enroll a total of 900 patients with relapsing MS from outpatient clinics and enrollment will be competitive. Sites include traditional academic centers as well as neurology practices so that a representative population of people with MS will be included in the study. It is projected that each site will enroll 20-40 patients over a 36 month enrollment period. The recruitment goals for this pragmatic trial are reasonable because almost all newly diagnosed patients will be eligible for participation, there is a great deal of decision-making that remains in the hands of the patient/clinician team, patients and stakeholders will help promote the trial, and the sites chosen all have a high volume of MS patients. **Training modules will be used to review important details of the study including recruitment strategies which study team members will be required to review. This information will also be covered during the virtual site initiation visits.**

Sites may use a number of approaches to enroll participants; for example, electronic health system software allows for the identification of MS patients who meet various characteristics. Traditional methods of screening participants for trial participation include educating prescribing providers, nurses and office staff to flag a patient for referral to the study so as to capture all patients who have been recently diagnosed with MS or prescribed a new MS medication; IRB-approved screening of charts of patients with upcoming appointments by study staff to identify those individuals who appear to meet criteria for enrollment; and education of community neurologists who routinely refer to MS specialists about the availability of the trial, as well as accommodating such eligible patients for quick screening visits so as to avoid therapeutic delays. In addition, at Johns Hopkins, patients will check out with research staff before leaving the building so that they can be assessed for candidacy for open research studies. This process could be adopted and will be encouraged at the other participating sites. We will directly contact patients of those who are covered by an IRB-approved HIPAA waiver or whose treating clinicians are on the study team; otherwise we will ask permission of treating clinicians. In addition, the National MS Society and Consortium of MS Centers, both stakeholders for this study, as well as our patient partners, will disseminate knowledge about the study and recruitment status via websites in order to reach the broadest and most representative sample of MS patients possible; and updated information about the study will be available on *www.clinicaltrials.gov*.

MS disproportionately affects women, and the increase in MS incidence has also occurred more in women.[78] While traditionally considered more common in white individuals, recent studies have shown a higher incidence in African Americans.[79,80] It is anticipated that more women (about 70%) than men will be enrolled. The cohort is projected to include individuals of other races and ethnicities, predominantly African Americans, as detailed in Table 7 below. MS is much less common in Native Americans, Hawaiian/Pacific Islanders, and Asian Americans, but every attempt will be made to consecutively recruit all patients initiating on eligible disease-modifying therapies who otherwise meet inclusion and exclusion criteria.

Table 7. Estimated Final Racial/Ethnic and Gender Enrollment Plan

Race	***Male (N)***	***Female (N)***	***Total (N)***
American Indian/Alaska Native	0	1	1
Asian	10	24	34
Black/African American	57	132	189

Hawaiian/Pacific Islander	0	2	2
White	175	409	584
Multiracial	27	63	90
Ethnicity	***Male (N)***	***Female (N)***	***Total (N)***
Hispanic (Latino/Latina)	26	64	90
Non-Hispanic	243	567	810

To promote high retention of study participants for the duration of the trial, the number of study visits has intentionally been limited to the standard of care so that patients will be seen on the same schedule they typically would be if they were not in a study. In order to strike a balance between the desire to collect more data and minimizing burden on enrolled patients, and being mindful that there are practice effects associated with some of the testing (e.g. cognitive testing), all of the outcomes will not be evaluated at each visit. Brain MRI will be conducted, per standard of care, at baseline and at months 6, 12, 24, 36, 48 and 60. Most of the PROs will be completed electronically between office visits so as to avoid questionnaire fatigue during visits. We will ask participants for several points of contact (email, phone, address, and contact information of 2-3 people who they expect will always be able to find them) so that if people change their phone number or move, we are able to find them and ask them to come back for semi-annual visits. Also, a small stipend will be paid for each in-person visit ($60) to help defray the costs of transportation and parking and $5 will be paid for each e-PRO completed to encourage full and continued participation. Only visits that participants attend in-person and questionnaires that are completed on-line will be reimbursed and payments will be discontinued if a participant withdraws from the study. The JHCC will pay sites based on milestones (visits and ePROs entered into the VISION™ EDC) and each site will be responsible for paying their participants per their institutional practice.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is randomization to a medication class rather than to any specific MS disease-modifying therapy. This protocol does not specify which medication within the medication class the treating physicians and the enrolled patients have to use during this trial. Of the medications that are in common use for MS in the community, the SAC has classified them as “traditional, first-line” or “higher-efficacy” for the purpose of this trial (see Table 4 on page 19). Only one of these medications, rituximab, is not FDA-approved for MS. Rituximab has been used off-label for MS for over a decade. It was shown in a phase 2 trial to be very effective for relapsing-remitting MS.[81] It is an anti-CD20 monoclonal antibody that was never tested in phase 3 trials. Instead, the company that manufactures it put ocrelizumab, a humanized form of the anti-CD20 antibody, through phase 3 trials. However, many people still choose to use rituximab due to their long experience using it in the standard of care setting, lower price, and potentially better safety record. Use of rituximab and the other FDA-approved

medications for MS in this study meets the requirements for exemption from IND regulations, as determined by the Food and Drug Administration (FDA). The justification for this determination was based on meeting all six of the below conditions:

According to *21 CFR 312.2(b)(1),* the clinical investigation of a *marketed* drug or biologic does not require submission of an IND if all six of the following conditions are met:

(i) it is not intended to be reported to FDA in support of a new indication, for use, or to support any other significant change in the labeling for the drug;
(ii) it is not intended to support a significant change in the advertising for the product;
(iii) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly INCREASES THE RISKS (or decreases the acceptability of the risks) associated with the use of the drug product;
(iv) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
(v) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
(vi) it does not intend to invoke 21 CFR 50.24.

In addition, new medications may become FDA-approved to treat RRMS during the trial and will be considered by the SAC to be classified as traditional or higher-efficacy medications for inclusion in the trial using consensus-based decision-making as was done at the first SAC meeting.[82-90] The SAC will meet by teleconference no later than a month out from FDA-approval of a new medication unless the need for a decision falls within a month of the annual in-person SAC meeting. If the SAC votes to include a new medication in the trial, and classifies it as traditional or higher-efficacy, the protocol will be revised and the new medication will be added to either the traditional or higher-efficacy list of medications in Table 4 (page 19). A change in research with a revised protocol and consent form will be submitted to the JHM IRB and only after approval of the new protocol, would the medication become part of the trial. Likewise, if any FDA-approved drug listed in Table 4 (page 19) is withdrawn from the market during the trial, it will be removed from the list of therapies found in the protocol and consent form. Currently classified medications will remain in their assigned medication class for the duration of the trial (i.e., no drug category changes will be made). After IRB approval, participants will be informed about the changes to the list of therapies for the study and re-consented at their next in-person visit to continue participation in the study. Participants may withdraw from the study at any time and this decision will not impact their relationship with their provider or the medical care they receive for their condition. As it seems unlikely that a currently unapproved medication would become a "standard of care" medication in the next two years without FDA approval, we anticipate only FDA-approved medications for RRMS will be considered for addition to the list of trial medications as standard of care medications, so no IND application or IND exemption determination will be needed during the trial.

6.1.2 DOSING AND ADMINISTRATION

Standard of care dosing is expected to be used for each drug, but as is consistent with a pragmatic trial, dosage adjustments made by local physicians/patients are permitted. For example, occasionally people reduce the frequency of taking one of the oral medications in order to avoid severe lymphopenia or side

effects like gastrointestinal distress. The protocol will not interfere with the practice of the provider in this regard, as such modifications would be consistent with an effectiveness, pragmatic trial. Prescribed dosage adjustments will be captured in the CRFs.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Not applicable

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Not applicable

6.2.3 PRODUCT STORAGE AND STABILITY

Not applicable

6.2.4 PREPARATION

Not applicable

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization in this study will be stratified by subgroups, whether a patient is considered at high-risk or low-risk of longer-term disability. Participants will be randomized, 1:1 within strata, to a higher-efficacy versus traditional, first-line therapy as classified by the SAC for the TREAT-MS Trial. This is a pragmatic trial, and neither treating physicians nor the participants will be blinded to the treatment they receive. However, the primary outcome is disability progression, as assessed by the EDSS+, and the EDSS examiner will be blinded to treatment, as will be the person administering the T25FWT and other elements of the MSFC, the cognitive tasks, and the visual assessment. The neuroimaging (MRI and OCT) outcomes will also be blindly evaluated.

The randomization scheme and algorithm will be created by the study statistician and embedded within the VISION™ EDC system which in turn will randomize the patients electronically once patient informed consent has been obtained and all inclusion criteria have been met. Participants will then receive their randomization information in real time so that the physician and participant can discuss the various treatment options within the class to which they are randomized and determine a treatment plan at that appointment. If safety tests are not completed yet and the person is determined ineligible based on the results of tests ordered at that visit, the randomization will be returned to the pool for reassignment. Likewise, if a participant is unable to obtain insurance authorization for a medication within the therapy class s/he has been randomized to or if a participant is enrolled in error based on inclusion/exclusion criteria (e.g., site learns after completing the baseline visit that the patient had received an MS disease-

modifying therapy in the 6 months preceding enrollment), the participant will be deemed a screen failure and the randomization slot returned to the pool for reassignment.

Low-risk patients initially randomized to traditional, first-line therapies but who experience breakthrough disease after 6 months on treatment and decide to switch, will be re-randomized through the VISION™ EDC system to either a different first-line therapy or to a higher efficacy therapy.

6.4 STUDY INTERVENTION COMPLIANCE

Medication adherence will be more easily assessed for the infused therapies than for self-administered medications since infusions are tracked easily in the electronic health record. Self-administered medication adherence will be tracked in an unobtrusive way, consistent with a pragmatic trial design.[74] Participants using self-administered medications will be asked to complete a simple medication adherence question at the time they are completing other PROs online, based on studies of self-reported medication adherence.[91,92] To minimize the impact of co-intervention, those randomized to infused therapies will also be asked a similar question about their adherence to infusion appointments at the same time points. Again, while it is likely that adherence may be better estimated for the higher-efficacy therapy groups than the first-line therapy groups and that this will lead to a less complete understanding of the mechanisms by which the self-administered medications are less effective (if this is a correct hypothesis), this issue is a "real world" one and is expected in pragmatic trials that are evaluating the effectiveness, rather than the efficacy, of these treatments in the broader population of people with MS. Thus, rigid quantification of adherence may not be necessary, as future MS patients are likely to encounter the same adherence challenges as those enrolled in this study. Also consistent with pragmatic trial design, site PI adherence to the protocol will be monitored largely for ensuring patients are appropriately risk-stratified and randomized in the first section; subsequently, monitoring will focus on ensuring data collection is being completed and data are entered.

Defining excess breakthrough activity: Patients and physicians may have various thresholds in tolerating breakthrough activity. The SAC determined that the Modified Rio Score[93] as outlined below will be used as a guideline for the maximum amount of disease activity (relapses/new lesions) that should be tolerated. This guideline will ensure that the site PIs realize that if a patient has passed this threshold, it is generally advised to counsel the patient to change the medication. To clarify, if a person has their "month 6" MRI scan AFTER 6 months on therapy, new lesions don't necessarily contribute to the "breakthrough" definition. Gadolinium-enhancing lesions could still count for this metric if the "month 6" MRI was completed after 7 months on therapy (as it would imply new disease activity after 6 months on therapy). Please see below for additional guidance on timing and interpretation of the "month 6" MRI.

The acquisition and timing of the "month 6" MRI is critical for the TREAT-MS study because:

- Patient is able to switch therapy for **ANY NEW** breakthrough disease occurring **AFTER 6** months on therapy.
- Doing the "month 6" MRI too early can reduce the ability to use it to support a claim for breakthrough disease.

If the "month 6" MRI is completed

- **≤ 6 months** after starting on therapy: For the subsequent MRI scan (designated as the month 12 scan when uploading), treating clinician will only be able to confirm a new lesion occurred "after 6 months on therapy" if the new lesion is enhancing.
- **> 6 months to 7 months** after starting on therapy: Scan can serve as a true reference MRI scan against which subsequent new lesions can be counted as occurring "after 6 months on therapy."
- **> 7 months** after starting on therapy: If a new lesion is present AND enhancing, treating clinician can assume it developed "after 6 months on therapy." If not enhancing, the MRI will simply be a reference MRI scan against which subsequent new lesions can be confirmed.

The Modified Rio Score[93] consists of an MRI criterion (>4 new T2 lesions=1 point) and a relapse criterion (1 relapse=1 point; 2 relapses=2 points).

a) Scores of 2 to 3= treatment non-response with respect to progression risk at 4 years.

b) The authors later re-classified those who scored 1 point (based on activity from months 12-18) into:

Medium-low risk (no relapses, <2 new MRI lesions)→ same as score of zero
Medium-high risk (≥1 relapse or ≥2 new MRI lesions) →same as score 2 or 3

TREAT-MS Trial Maximum Tolerated Modified Rio Score

End of Year 1: a Modified Rio Score of 2-3, or score of 1 if in "medium-high" risk subgroup

End of Year 2:

a) if prior Modified Rio Score was medium-low risk (at year 1): anything more than 1 additional T2 hyperintensity at year 2 MRI (or earlier in year 2 if a relapse occurs prior to the year-end visit)
b) if Year 1 Modified Rio Score was 0, a Modified Rio Score of "medium-high risk" or greater

Subsequent years will be treated in the same fashion. For example, at the end of year 3:

a) if prior Modified Rio Score was medium-low risk (at year 2): anything more than 1 additional T2 hyperintensity by year 3 end (or earlier in year 3 if a relapse occurs prior to the year-end visit)
b) if Year 2 Modified Rio Score (at year 2) was 0, a Modified Rio Score of "medium-high risk" or greater

6.5 CONCOMITANT THERAPY

Number of new medications, escalated dosage of medications and non-pharmacologic interventions for MS-related symptoms will be collected as concomitant medications or therapy as an exploratory (tertiary) outcome. The number of newly-prescribed or dose-escalated medications used for treating MS symptoms (including pain, weakness, numbness/tingling, trouble walking, cognitive problems, fatigue, depression, anxiety, visual dysfunction, spasticity, vertigo, or bladder/bowel/sexual dysfunction) during the trial will be evaluated using the electronic health record. The final list of medications that will be considered as symptomatic therapies was approved by the SAC and includes all of the pharmacologic therapies identified in the PCORI multi-stakeholder group meeting (see section 10.2 Additional Considerations (Appendix)).[71] The rationale for this outcome is that medication burden may be a gauge

of symptom burden in patients with MS, in whom polypharmacy is associated with reduced health-related quality of life.[72]

6.5.1 RESCUE MEDICINE

Not applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The study intervention is randomization to a medication class, so discontinuation from study intervention equates to choosing a medication from a different efficacy class (e.g., choosing a first-line therapy when patient was randomized to a higher-efficacy therapy). Participants who discontinue therapies for reasons other than breakthrough disease (e.g. intolerance, adverse effect, desire to conceive) will be encouraged (except in the instance of trying to conceive or pregnancy itself, or when such treatment is otherwise contraindicated) to choose another therapy within the efficacy class (higher-efficacy versus first-line) to which the discontinued therapy belongs. These patients will be analyzed by intent to treat, regardless of whether this recommendation is followed. All patients randomized and started on treatment will be followed in the study, with data collected both in-person and electronically, even if their treatment deviates from their randomized assignment.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the CRF. Subjects who sign the informed consent form and are randomized but are determined ineligible based on the results of tests ordered at that visit will be replaced. Likewise, if a participant is unable to obtain insurance authorization for a medication within the therapy class s/he has been randomized to within 90 days of randomization (absent an administrative delay or other reason that is expected to be easily resolvable), the participant will be deemed a screen failure and will be replaced. Subjects who sign the informed consent form, and are randomized to a medication class, and subsequently withdraw, or are withdrawn or discontinued from the study after starting a medication from the assigned medication class, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 month of the missed visits, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study. Attempts to reschedule the missed visit will continue up to 3 months after the target visit date. Beyond 3 months, the visit will be considered missed and the visit window for the next standard of care clinic visit will open.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and at least 2 attempts to reach each of their emergency contacts and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
  Should the participant continue to be unreachable (3 consecutive visits missed and no response to repeated attempts to contact), he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up. If a participant no longer wishes to return to the site for his/her MS care, but is willing to complete ePROs, investigators will encourage continuation in the study as a virtual participant as their input is valued since the long term vision is to follow participants beyond 5 years.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFECTIVENESS ASSESSMENTS

Following the informed consent process, patients who have given consent to participate in the study will be evaluated for eligibility to enroll in the study and be randomized. Screening assessments include review of the medical chart and collection of data for demographic, medical/surgical history, MS and relapse history, laboratory, and prior MS medication inclusion/exclusion criteria as detailed in the study's manual of procedures (MOP). In addition, review of radiologic findings is necessary to confirm eligibility and allow for risk classification that takes place prior to randomization.

Once a participant is deemed eligible for the TREAT-MS trial and has been classified as being at higher or lower risk of disability progression, randomization is requested through the study's VISION^{TM} EDC system. Eligible participants are randomized 1:1 within risk strata to a traditional MS therapy versus a higher-efficacy therapy as categorized for the study (Table 4 on page 19). Patients will then receive their randomization information in real time so that the physician and patient can discuss the various treatment options within the class to which they are randomized and determine a treatment plan at that appointment.

The screening/baseline visit will continue with exams and assessments to capture primary, secondary and tertiary outcome measures. Evaluations that contribute to the primary endpoint (EDSS and two specific components of the MSFC, the T25FWT and the 9HPT) will be performed by qualified personnel who are blinded to the participant's risk stratification, medication class and specific DMT chosen. The examining physician will complete a blinded neurological exam to calculate the EDSS and a blinded coordinator will complete the MSFC, low contrast visual acuity and the SDMT. The primary coordinator will collect confidential contact information and concomitant medications as well as educate the participant about the in-person and electronic PRO questionnaires that will be completed over the course of the study. A baseline brain MRI will be completed, if a recent standard of care MRI has not been done, and OCTs will be obtained if considered standard of care at the participating site. Information from an MRI and OCT survey completed by the site prior to site activation will allow for customization of site specific consent form language for standard of care procedures.

Consented participants in the TREAT-MS trial (if at a site that has agreed to participate in the optional biobanking substudy), will be approached at this visit for consent to participate in the optional biobanking substudy. Subjects participating in the trial are not required to participate in the biobanking substudy. After consent is obtained, approximately 80 ml of blood will be obtained from each individual at baseline by venipuncture (5 green-top tubes [for immune cell studies and plasma for known, room-temperature stable studies], 1 purple-top tube [for DNA]), and 2 red-top tubes [for frozen serum]). An additional 70 mL of blood will be taken at the month 6 visit (or at the subsequent visit, if this one is missed; same tubes except no DNA), at the time of every switch of MS therapy (if due to breakthrough disease activity), and at end of study to evaluate for treatment response. All fresh samples will be shipped to the laboratory of Dr. Chander Raman at the University of Alabama at Birmingham Center for Clinical and Translational Science; frozen samples will be shipped to the Johns Hopkins Coordinating Center once the final consented patient at a given site has completed the second blood draw and then again at the end of the study.

Treatment with the chosen DMT will commence following insurance approval and receipt of medication. Follow-ups will coincide with routine clinic visits, when possible, to adhere to PCORI guidance for pragmatic trials. Traditionally, people with MS are evaluated in clinic every 6 months. The study windows will be more lenient than for a traditional explanatory trial and were established by the SAC as +/- 3 months of target visit date (contiguous windows) to ensure every visit counts. In order to strike a balance between the desire to collect more data and minimizing burden on enrolled patients, and being mindful that there are practice effects associated with some of the testing (e.g. cognitive testing), all outcomes will not be evaluated at each visit. Follow-up brain MRIs will be conducted, per standard of care, at months 6, 12, 24, 36, 48 and 60. Follow-up OCTs (if standard of care) will be obtained annually. Most of the PROs will be completed electronically between office visits so as to avoid questionnaire fatigue during visits.

Serious adverse events (clinically significant infections, malignancies, or the development of other serious comorbidities, as well as unplanned hospitalizations [for non-elective issues other than MS relapse] and death), or other adverse events (AEs) meaningful enough to lead to medication discontinuation will be noted in the progress note and collected as a secondary outcome. More detail on AEs and SAEs is found in section 8.3 and in the study's MOP.

8.2 SAFETY AND OTHER ASSESSMENTS

The main eligibility safety labs required for participants include either JC virus antibody negative or low positive (index antibody titer <0.9), or being negative for Hepatitis B and C, and tuberculosis (see inclusion section 5.1 for full details). Also, HIV testing must be negative because most clinicians would not use higher-efficacy therapies in the HIV-positive population due to possible infectious risks. Moreover, subjects need to be safe to take ≥ 1 higher-efficacy therapy in order to be eligible for randomization to that arm of the study.

Standard of care pre-screening and monitoring labs and diagnostic studies (outside of above) will be suggested and recommended per the individual medication's FDA-approved full prescribing information. The prescribing information for the various DMTs can be found in the study's MOP appendix.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign, symptom (or abnormal laboratory test), or disease temporally associated with the use of a medicinal product or *intervention*, whether or not it is considered related to the product/intervention. Collating all the AEs experienced by participants for each MS-specific disease-modifying therapies is out of the scope of this trial, and thus AEs will largely be reportable to appropriate authorities under the auspices of usual care. For purposes of the trial and assessing AEs as an outcome of interest to patients and stakeholders, however, serious adverse events (SAEs), as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (excluding elective admissions and admissions for MS relapse) will be recorded and reported. AEs that lead to discontinuation of a treatment or dose reduction also will be recorded and reported, since that seemingly represents an outcome that improves patient well-being. Treating physicians will record the relevant AEs and SAEs in the study database and will treat participants with AEs appropriately, per usual care. AEs will be collected from the start of the study (e.g., baseline visit/randomization) until a participant terminates from the study; those that are unresolved at the time of termination will be followed until they resolve or up to 30 days.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse events, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (excluding elective admissions and admissions for MS relapse) will be recorded and reported in this trial as detailed below.

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization (excluding elective admissions and admissions for MS relapse), a persistent or significant incapacity or substantial disruption of the

ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events, although not specific to MS, include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Since the intervention is randomization to a medication CLASS and the individual physician/study participant team will choose the specific medication to use within that class, adverse reactions to a specific medication will not be considered related to the study intervention. Therefore, there is no expectation that any adverse event will be related to the study intervention.

8.3.3.3 EXPECTEDNESS

Not applicable

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF if they lead to a decision to switch therapies or dose reduction. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to

specific treatment (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All reportable AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline medical history and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE if it leads to a decision to switch therapies or dose reduction or becomes an SAE.

Changes in the severity of a reportable AE will be documented to facilitate reporting at each level of severity.

Treating physicians will record all reportable events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will document the occurrence of reportable AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization, or up to 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.3.5 ADVERSE EVENT REPORTING

Adverse events that lead to a decision to switch therapies or dose reduction will be reported within 10 business days in the VISION™ EDC system. Specific details regarding AE reporting are included in the MOP. Reportable AEs will be summarized in twice yearly reports to the Data and Safety Monitoring Board (DSMB), and these reports will be submitted to the central IRB within 30 days of receipt of the final DSMB report/determinations by the study team. All DSMB meeting minutes will be documented in writing, signed by the DSMB chair, and then shared with the central IRB and study sites.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The treating physician will promptly report to the Johns Hopkins Coordinating Center (JHCC) and if warranted, the appropriate pharmaceutical company, any serious adverse event.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the JHCC and should be provided as soon as possible.

The treating physician will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction according to standard MedWatch reporting for marketed drugs under the auspices of usual care.

The following process for reporting an SAE will ensure compliance with the International Conference on Harmonisation guidelines: the reviewing Institutional Review Board (IRB) and Data and Safety Monitoring Board (DSMB) will be notified as soon as possible after the local PI learns of the event, but in all cases within ten business days of an SAE that is *intervention*/study-related and unexpected, or if the event is serious, expected and *intervention*-related, serious, expected and not *intervention*-related, or

serious, unexpected and not *intervention*-related (where, in this study, the intervention is randomization to higher-efficacy vs. first-line therapy). The death of a research participant must be reported promptly but no later than 3 business days of learning of the death if the death is unexpected and no later than 10 business days if the death is expected.

If the JHCC is informed that a participant has died within 30 days of receiving a study intervention at any site of the research (whether at Johns Hopkins or at another site), the JHCC must promptly inform the PIs at all of the participating study sites.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Since both MRIs and OCTs (if applicable at participating site) will be obtained as standard of care procedures, interpretations and documentation in the medical record of radiologic and imaging findings, including incidental findings, will also be standard of care. No additional reads for incidental or other findings will be reported by the image processing lab at JHU, as all analyses of MRIs and OCTs in this lab will be for research purposes only.

To respect the decision made by study participants who volunteer to take part in the study, the results of the study will be returned to all research participants in the form of a lay summary at the completion of the study. At the start of the study, each participant will be surveyed for their individual preference for communication of results and be allowed to choose from email, standard mail, telephone, or in person. This document will provide a summary of results of the research in lay terms which will be understandable and hopefully meaningful to the patient participants and their partner stakeholders.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable

8.3.9 REPORTING OF PREGNANCY

If pregnancy occurs during the study, it is recommended that the treating physician advise the participant to discontinue their MS medication if other than glatiramer acetate, which is considered safe (category B) to administer throughout pregnancy. Pregnancies will be captured as a reportable AE for tracking purposes. Pregnant participants will continue to be followed in the trial and all pregnancies will be followed to the pregnancy outcome, including ascertaining the development of serious adverse events (in the same fashion as for trial participants continuing on therapy; excluding the planned hospitalization for delivery) as well as the health status of the newborn at birth (but not beyond delivery day). Some standard of care procedures may be omitted (e.g., MRIs), but other research procedures (e.g. examination-based and PROs) may be performed if the participant is willing to complete them. Pregnancies will be reported by the treating physician in the VISION^{TM} EDC system within 10 business days of learning of the event.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The TREAT-MS study and Johns Hopkins Medicine IRB considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated problems are expected to be rare in this pragmatic trial since research procedures are conducted at standard of care visits. The VISION™ EDC system will capture unanticipated problems reported at the discretion of the site PIs.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the JHCC. The UP report will include the following information:

- Protocol identifying information: JHM IRB protocol title and number and site PI's name;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are deaths will be reported to the reviewing IRB and to the JHCC as soon as possible and no later than 3 business days after the investigator becomes aware of the event.
- Any other UP will be reported to the reviewing IRB and to the JHCC as soon as possible, but in all cases within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate site institutional officials (as required by an institution's written reporting procedures), within the time frame that is in accordance with site

institutional policy after the reviewing IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

If an unanticipated problem involving risks to participants or others results in revision to the consent form, participants will be re-consented at their next in-person visit to continue participation in the study. Participants may withdraw from the study at any time and this decision will not impact their relationship with their provider or the medical care they receive for their condition.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

The primary endpoint is **time to sustained disability progression**, as measured by the **Expanded Disability Status Scale plus (EDSS+):** a composite endpoint that includes EDSS change (change at any 6 month time point of $\geq$ 1.0 point if baseline EDSS is $\leq$ 5.5, or of $\geq$ 0.5 point if baseline EDSS $\geq$ 6.0, that is sustained 6 months later) **OR** 20% worsening on **either** of two specific components of the Multiple Sclerosis Functional Composite (MSFC), the timed 25-foot walk test (T25FWT) and the nine hole peg test (9HPT) that is sustained 6 months later.

The main hypothesis is that intermediate-term disability will be reduced by earlier use of higher-efficacy medications.

- Secondary Endpoint(s):

Patient-Determined Disease Steps (PDDS): This PRO is a self-assessment scale of MS disease status.

MSFC: The original MSFC consists of the Paced Auditory Serial Addition Test (PASAT), the 9-hole peg test, and the timed 25-foot walk test; low-contrast letter acuity (binocular, 2.5% contrast Sloan charts) will also be included and both composite MSFC and individual scores will be evaluated.

Relapse recovery: Among participants identified to have a relapse, relapse recovery will be defined as complete or incomplete based on a) patient self-report, and 2) neurologic examination (those who have increased Functional System scores, corresponding to the relapse symptoms, of 1.0 points or greater for at least 6 months after the relapse onset, without subsequent accrual of worsening in that same Functional System (e.g. more indicative of progression), will be considered to have incomplete relapse recovery).

Cognition using Symbol Digit Modalities Test (SDMT): The SDMT is commonly used in MS to assess processing speed and will be administered orally and used to evaluate changes in cognition throughout the study.

Multiple Sclerosis Impact Scale (MSIS-29): The MSIS-29 will be used to evaluate the impact of MS on the participants.

Quality of Life in Neurological Disorders (Neuro-QoL): The Neuro-QoL will be administered as an electronic PRO to capture health-related quality of life. Neuro-QoL includes subscales that capture depression and fatigue.

Social status: The incidence of change in employment to "disabled" or "looking for work, unemployed," using the NINDS MS Common Data Elements template, will be evaluated in all participants as an electronic PRO. Incident divorce or separation, among those who previously were married or in a domestic partnership, will likewise be captured.

Serious Adverse Events (SAEs): Serious adverse events (clinically significant infections, malignancies, or the development of other serious comorbidities, as well as unplanned hospitalizations [for non-elective issues, excluding MS relapse] and death), or other adverse events meaningful enough to lead to medication discontinuation will be noted in the progress note and collected as a secondary outcome.

9.2 SAMPLE SIZE DETERMINATION

Based on alemtuzumab extension data at 5 years,[19] sample sizes were calculated such that the study will have 80% power (assuming two-sided test and controlling type 1 error at 0.05) to detect a 10% difference for high efficacy vs. low efficacy groups (21% versus 31% who attain sustained disability progression). Under these assumptions, 321 patients will be needed per group. Only 60% of the alemtuzumab trial's study patients actually agreed to enroll in the extension study. We assume since the proposed study is more pragmatic, retention will be higher, but to account for potential drop-outs and also to have greater power to evaluate differences in treatment effects between subgroups as well as the effects of switching treatments (secondary analyses), we will enroll 450 patients per group (see Table 8. Recruitment Plan below). This sample size gives us 80% power to detect a hazard ratio of 0.7 for time to sustained disability progression.

Table 8. Recruitment Plan

Total number of study participants expected to be screened:	1,200
Of those screened, total number of study participants expected to be eligible:	1,100
Of those eligible, total number of study participants enrolled:	900
Target sample size *(i.e., of those eligible, total number of study participants expected to be enrolled)*:	900

9.3 POPULATIONS FOR ANALYSES

The primary analysis will be to evaluate the impact of treatment arm assignment (traditional, first-line versus higher-efficacy therapy) on the time to sustained disability progression during the course of the trial. The primary analysis for the trial will be conducted by intention-to-treat (ITT, according to the arm to which patients were originally assigned).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The primary outcome is time to sustained disability progression, which requires methods for censored data (subjects who have not progressed by the end of follow up may progress after the study ends; these are censored observations whose time to progression is unknown other than that it is greater than the follow up period). Special statistical methods are required to deal with censored data. The primary hypothesis test will incorporate baseline covariates in order to increase efficiency and will answer the question, “did the control group tend to exhibit more progression within a particular time window (to be determined by the follow-up times observed during the study) than the treatment group?” As a secondary analysis we will conduct a nonparametric log-rank or Wilcoxon test, which will answer the question "did the control group tend to progress sooner than the treatment group?” This test has the advantage of being fully nonparametric--it makes no assumptions about the distribution of the survival times. To explore effect modification by measured risk-factors we will use (semi-) parametric survival models like the Cox proportional hazards (PH) model and accelerated failure time (AFT) model, further detailed below.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary analysis will be to evaluate the impact of treatment arm assignment (first-line versus higher-efficacy therapy) on the time to sustained disability progression during the course of the trial. The primary analysis for the trial will be conducted by intention to treat (e.g. according to the arm to which patients were originally assigned). Since the sample size is large and the trial randomized, including a stratification surrounding risk factors for longer-term disability, we anticipate that putative confounders will be equally distributed between the groups. However, incorporating baseline predictors of the outcome can substantially increase the power and efficiency of statistical tests, and for that reason our primary analysis will take them into consideration in a restricted mean survival time model.[94] As a sensitivity analysis we will also perform a fully non-parametric and unadjusted test for statistical significance between treatment arm assignment groups using the log-rank test, if the proportional hazards assumption holds, or the Wilcoxon test, if it does not, and construct corresponding Kaplan Meier curves. As a secondary analysis we will include potential effect modifiers in a multivariate model (either a Cox proportional hazards model or an accelerated failure time (AFT) model depending on which fits the data better) to evaluate their impact on the relationship between treatment type and disability. Further, we will evaluate in the pre-identified subgroups (high-risk versus low-risk for disability) whether the magnitude of the effect is similar or if, as hypothesized, early higher-efficacy treatment has a greater intermediate-term impact on sustained disability progression in those thought to carry greater risk for long-term disability.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

We will evaluate, among those who switch from first-line therapy after breakthrough disease to either higher-efficacy versus a different first-line therapy, whether there is a difference in risk of sustained disability progression, again using nonparametric, Cox proportional hazards, and AFT models.

The risk of sustained disability progression will also be evaluated in additional sensitivity analyses, including in those randomized to higher-efficacy therapy compared to those who were initially on first-line therapies but switched due to breakthrough disease, in order to assess if there is a meaningful difference in these treatment strategies. Although the primary analyses will be ITT, those who start on first-line therapy but switch to higher-efficacy therapy due to breakthrough disease contribute patient-time to first-line as well as higher-efficacy therapies. As such, secondary analyses will address the effect of treatment received using propensity score methods (marginal structural models) and structural nested models to control for confounding.[95] Additional analyses will assess the assumptions that led to the determinants of long-term disability risk by evaluating if in fact those pre-determined factors were indeed predictive of sustained disability and whether, at the level of each of the included factors, there is a specific factor or set of factors that appears to most highly suggest a benefit of early use of higher-efficacy therapies.

Secondary and tertiary outcomes will initially be compared among the two primary treatment groups (higher-efficacy versus first-line) by intent to treat, utilizing Cox proportional hazards and AFT models (time to worsening PDDS or MSFC), mixed-effects regression models (change in scores for cognition, fatigue, health-related quality of life, low-contrast letter acuity, retinal nerve fiber layer thickness [as well as segmented and total macular volumes on OCT], brain volume change [e.g. gray matter volume, cortical thickness]), or generalized estimating equations (Poisson models for number of relapses; binomial models for relapse recovery and, change in social status among those previously employed or married or in a partnership; negative binomial models for number of MS-related symptomatic medications and number of new T2-weighted hyperintensities). The incidence of adverse events will be recorded by system, severity, and by relationship to treatment arm. Since the correlations among outcomes will likely be very high, making adjustments for multiple comparisons is likely excessively conservative and thus is not planned.

Missing data: As above, every effort will be made to *prevent* missing data so as to avoid associated bias and reductions in power. However, inevitably data missingness does occur. From the perspective of ensuring adequate power, because it's longer than most trials, we assumed a 20% dropout rate (higher than typical) in calculating the sample size. For the analyses, we will evaluate the impact of missing outcome data in several ways, including imputation (particularly since we will collect PDDS at all the same time points as EDSS, relevant given correlation-- $\rho = 0.78$),[47] and presenting the results of the treatment effect on outcomes when data are censored, when last observation is carried forward, or en

treatment failure or success are assumed of missing data. We will also apply to work with PCORI-funded researchers at Johns Hopkins to use their global sensitivity analysis tool to evaluate the impact of missing data on the results.[96] The impact of the modeling assumptions on the results will be presented in the primary manuscript for the trial.

9.4.4 SAFETY ANALYSES

Adverse events leading to a decision to switch therapies or dose reduction and serious treatment-emergent AEs will be presented in table format. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), counted once only per switch of DMT for a given participant and severity and relationship to treatment arm will be presented by System Organ Class (SOC) and preferred term groupings.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Not applicable

9.4.6 PLANNED INTERIM ANALYSES

Not applicable

9.4.7 SUB-GROUP ANALYSES

Not applicable

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will focus on tertiary outcomes below:

Brain MRI evidence of neurodegeneration: Changes in brain MRI measures of neurodegeneration, including whole brain and normalized gray matter volumes as well as newer metrics such as cortical thickness and subcortical gray matter compartment volumes, and measures of T2 lesion burden, will be assessed. MRI protocols will be standardized and loaded onto clinical scanners at one or more MRI facilities associated with each participating site and volunteers will be recruited and consented to participate in test run MRIs (without contrast) for quality control purposes. Because these test MRIs are not considered part of this research, local site requirements for the conduct of these test MRIs will be followed.
Relapses: The number of relapses (new or worsening neurologic symptoms lasting for 24 hours or more in the absence of fever) will be assessed.

New brain lesions: The number of new/enlarging T2-weighted hyperintense lesions and T1-weighted hypointense lesions will be quantified on each scan.
Optical coherence tomography (OCT): Retinal nerve fiber layer and ganglion cell/inner plexiform thickness will be evaluated among patients at centers with access to OCT as standard of care.

As an additional exploratory outcome, the number of newly-prescribed or dose-escalated medications used for treating MS symptoms (including pain, weakness, numbness/tingling, trouble walking, cognitive problems, fatigue, depression, anxiety, visual dysfunction, spasticity, vertigo, or bladder/bowel/sexual dysfunction) during the trial will be evaluated using the electronic health record. The final list of medications that will be considered as symptomatic therapies was approved by the SAC and includes all of the pharmacologic therapies identified in the PCORI multi-stakeholder group meeting (see section 10.2 Additional Considerations (Appendix)).[71] The rationale for this outcome is that medication burden may be a gauge of symptom burden in patients with MS, in whom polypharmacy is associated with reduced health-related quality of life.[72] In addition, non-pharmacologic interventions (and referrals to other healthcare providers) for symptom management will also be captured.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. The following consent materials are submitted with this protocol: Research Consent form template for all sites, Johns Hopkins Study Site Information document, telephone screening script, HIPAA waiver for chart screening.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without

prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date and time of consent), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If a patient is language or hearing impaired, an interpreter or sign language communication will be utilized to overcome these impediments.

The study is not specifically targeting non-English speakers for this trial. If more than an occasional person speaking the same non-English language will likely be enrolled at a particular site due to patient demographic differences, a fully translated informed consent form will be developed. If needed, this translated consent form and certificate of translation will be submitted to the JHM IRB for review after JHM IRB approval of the English version of the informed consent document.

Assessment of Comprehension of Study Protocol and Consent for Study Participation

Study team members participating in the consent process will conduct a post-consent discussion with each candidate using the below questions as a guide for reviewing important points and correcting potential misunderstandings.

- Does this study provide medication free of charge?
- Does everyone receive the same treatment in this study?
- What is the main difference between the two arms of this study?
- How long will you be in this study?
- What extra visits does this study require beyond the usual clinical care visits?
- If you cannot tolerate the first medication, can you change to any other medication, or will your doctor provide you with a specific list of options?
- Which patients have a chance of a second randomization?
- Will you be paid for participating in this study?
- Which procedures will be billed to you or your insurance?
- Which procedures will be for research only and will be provided at no cost?
- Are you able to withdraw at any time from participation, at no penalty?

The documentation of consent process will be formalized with answers to the above questions noted on a supplemental study document ("**Documentation of Consent Process for TREAT-MS Trial**"). If the initial response is not correct to any of the questions, the consent designee will re-explain that information so the potential participant understands. All questions listed above will be asked and responses to each question will be documented, including whether the initial response was correct, and (if not) that the item was explained to the potential participant's understanding.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

Not applicable

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their partners. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the Institutional Review Board (IRB), may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the VISION™ web-based EDC to be accessed by study team personnel and their partners at the JHCC. These data will include the participant's name, date of birth, medical record number and other identifying information, such as labs, progress notes from clinic visits, MRIs and OCTs. While for CRF data, individual participants and their research data will be identified by a unique study identification number, identifiable images and medical record source data will be uploaded to the VISION™ EDC without first being de-identified. The study data entry and study management systems used by clinical sites and by JHCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the JHCC.

10.1.4 FUTURE USE OF STORED DATA

Data collected for this study will initially be stored and managed in a web-based platform called VISION™, an FDA- and HIPAA-compliant comprehensive clinical trial and clinical data management system developed by Prelude Dynamics, LLC, a company based in Austin, Texas. In addition to its electronic data collection (EDC) capabilities for clinical trial case report form data, it has the capacity for source document storage and essential document maintenance, and permits direct collection of e-PRO questionnaire data from trial participants. Access is controlled by permission-based, secure user IDs and passwords and is limited to select forms and functionality based on user roles. Data will be downloaded

as SAS transport files or the equivalent for analysis by the study statistician on Johns Hopkins Bloomberg School of Public Health secure servers.

Imaging data will be stored in the VISION™ database initially and then transferred to secure servers at Dr. Jerry Prince's Image Analysis and Communications Lab (IACL), part of the Center for Imaging Science at the Johns Hopkins University's Homewood Campus. Dr. Prince's lab will process and analyze MRI and OCT data, but will not read the images for incidental findings or provide any individual level reports to inform clinical care. Standard of care readings of both MRIs and OCTs are the responsibility of the local sites/providers and these reports will also be shared with the study for research purposes.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Study Leadership and Study Advisory Committee (SAC)

Study Leadership

Co-Principal Investigator	**Co-Principal Investigator**
Ellen M. Mowry, MD, MCR	Scott D. Newsome, DO
Johns Hopkins University School of Medicine	Johns Hopkins University School of Medicine
600 N. Wolfe Street, Pathology 627 Baltimore, MD 21287	600 N. Wolfe Street, Pathology 627 Baltimore, MD 21287
410-614-1522	410-614-1522
emowry1@jhmi.edu	snewsom2@jhmi.edu

Study Advisory Committee (SAC)

As is characteristic of a pragmatic trial conducted in the standard of care setting, great autonomy for the patient/provider team will be maintained in the TREAT-MS trial. Nevertheless, the trial is guided by a SAC that includes a number of different stakeholders: members of the MS community, including clinicians (site PIs or their designees), biostatisticians and patients/partners as well as representatives of key organizations including major payers, the National MS Society and the Consortium of MS Centers. The individuals who attended the first SAC meeting in October 2017 were critical to the design of several key aspects of the study, including the two most critical ones: determining which therapies are "higher efficacy" or "traditional" and also determining which patient characteristics will discriminate a "high risk" versus "low risk" individual. These decisions, as well as finalization of the primary outcome, formed the fundamental backbone of the trial and will influence the long-term impact of the study greatly. The decisions were made by a consensus-based approach and this approach will be used for subsequent trial/protocol decisions. The SAC will meet twice yearly, once in-person and once by teleconference, throughout the trial, as well as anytime the Data and Safety Monitoring Board (DSMB) makes a recommendation or one/more SAC members raises concerns, to review trial progress and consider the inclusion and classification of any new FDA-approved MS medications. **We anticipate utilizing a consensus approach, as we did for the initial SAC meeting, to make decisions regarding protocol modification or medication classifications.**

10.1.6 SAFETY OVERSIGHT

Safety oversight is under the direction of a DSMB, responsible for monitoring the ethical conduct of the **TR**aditional versus **E**arly **A**ggressive **T**herapy for **M**ultiple **S**clerosis (**TREAT-MS**) trial and for monitoring the accumulating data for quality and evidence of adverse findings. The DSMB reports to the study Co-Principal Investigators (Co-PIs) who serve as ex officio non-voting members of the DSMB, as well as the SAC. Members of the DSMB are independent from the study conduct and free of conflict of interest, or measures are in place to minimize perceived conflict of interest.

The voting members are appointed by the study Co-PIs and the TREAT-MS DSMB consists of individuals with the appropriate expertise, including a clinical trial biostatistician (Dr. Gary Cutter), an MS neurologist (Dr. Jiwon Oh), a neuroinfectious disease specialist (Dr. Joseph Berger), and a patient representative (TBD). Dr. Oh has an adjunct position at JHU but practices out of the University of Toronto, Canada. The DSMB voting members will determine which member will serve as the chairperson prior to the first organizational meeting. Members who miss two consecutive meetings are subject to replacement at the request of the DSMB Chairperson. Prior to the first meeting, all members are expected to file conflict of interest statements with the DSMB Chairperson that describe any personal or professional involvements with manufacturers or others who might benefit financially from the conduct of or findings from the TREAT-MS trial.

In addition to the voting members, the DSMB also includes non-voting members who serve by virtue of their special roles in the study. These ex officio members are:

- Director of the TREAT-MS trial
- TREAT-MS biostatistician

Other Johns Hopkins Coordinating Center (JHCC) investigators, staff, and consulting investigators may participate in the open portion of DSMB meetings as observers or to provide information relevant to DSMB discussions at the invitation of or with the approval of the DSMB Chairperson. The chairperson of the DSMB may invite other individuals to attend one or more open or closed sessions of meetings in order to advise the DSMB when necessary for proper interpretation of the data.

The study is unusual in that the intervention in this case is randomization to a CLASS of medications. Thus, while SAEs as well as AEs substantial enough to lead to/be a major contributor to discontinuation of a medication (as these will be outcomes in the trial) will be collected, we will not collect all AEs associated with each product being used. It is likely that there will be AEs and SAEs, but in reality, the likelihood that these will be related specifically to the randomization is quite low. If the DSMB has recommendations about protocol modifications, those will be submitted to the SAC for consideration,

either at its biannual meeting or under a specially-convened teleconference, as recommended by the DSMB.

Briefly, the DSMB is expected to review cumulative AEs and SAEs, their relationship to the intervention (randomization to a class of medications) and recommend if the trial should proceed without changes or if modifications to the protocol should be considered by the SAC. Protocol modifications suggested by the DSMB will be considered and voted on by the SAC, using the same consensus-based approach as adopted at the first SAC meeting, prior to submitting to the central IRB as a change in research.

The specific functions of the DSMB are to:

- Assure that the TREAT-MS trial is conducted in accordance with current ethical standards.
- Evaluate the accumulating data at regular intervals for evidence of adverse effects.
- Recommend to the SAC changes in the TREAT-MS trial protocol based on periodic data analysis.
- Advise the study Co-PIs and SAC regarding issues related to TREAT-MS policy or conduct.
- Advise the TREAT-MS trial SAC regarding procedural or ethical issues.
- Assess overall data quality and evaluate the impact on interpretation of the TREAT-MS trial data.
- Advise the TREAT-MS trial Co-PIs and SAC regarding problems encountered in the conduct of the study, whenever requested to do so.

The DSMB will meet as frequently as necessary but at least twice yearly by teleconference or in person. Data reports will be provided by the JHCC in advance of each meeting. Additional meetings and reports are scheduled as requested. The JHCC is responsible for preparing the minutes of the DSMB meetings.

10.1.7 CLINICAL MONITORING

Remote clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Sites will complete surveys and site personnel will provide documentation of experience and training to perform the trial duties as delegated by the site PIs.
- Webinars will be conducted to train site personnel on the protocol and research procedures prior to site activation.
- JHCC will conduct the centralized monitoring throughout the study by targeted review of certain data, including targeted data verification of endpoint, safety and other key data variables and the preparation and distribution of DSMB reports.
- The VISION^{TM} EDC system has built in range checks and automated queries to aid data managers at the JHCC in monitoring activities.
- Uploaded source data will be compared to entered data and double-data entry will be employed for key variables.

- Further details of the monitoring plan, including the risk assessment and mitigation plan, are found in the MOP.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database and will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The JHCC will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.
The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of remote monitoring and auditing by the JHCC, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets, case report forms (CRFs) will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic CRF (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the VISION electronic data collection system (Prelude Dynamics Inc., Austin, Texas, www.PreludeDynamics.com*),* a 21 CFR Part 11-compliant data capture system hosted from an encrypted database server located in an access-controlled tier-1 commercial data center (OnRamp, Austin, TX, www.onr.com). The server is protected by multiple T1 connections, battery, and generator backups, and redundant climate controls with daily back-ups. Prelude maintains a similar redundant Data Center relationship (omegabyte.com) for use as a backup

facility, and this facility is able to quickly assume hosting responsibility in the event that the server fails at the original hosting center.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. VISION also provides a repository for source documents and imaging uploads via a secure cloud transfer.

Sites will have access to records for only their participants and JHCC data management personnel will have access to records across all sites and protected health information (PHI) for all participants.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained until at least 2 years have elapsed since the formal discontinuation of the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the JHCC. It is the responsibility of the JHCC to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the Johns Hopkins Coordinating Center. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. The manuscripts that are generated as a result of this trial will include all of the recommended CONSORT guidelines as well as the extension items recommended for pragmatic trials.[97,98] In addition, to the greatest extent possible, adherence to these standards will also be translated, with input from the

patients and stakeholders, into patient-friendly language that can be used as part of the dissemination strategy. Details of the publication policy will be described in the study's MOP.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the Patient-Centered Outcomes Research Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS (APPENDIX)

Treatment Options for MS Symptoms

Symptom	Pharmacologic Treatments	Non-pharmacologic Treatments
Fatigue	Amantadine, armodafinil, methylphenidate, selective serotonin reuptake inhibitors (SSRIs), aspirin, modafinil, dextroamphetamine salts, lisdexamfetamine, fluoxetine, pemoline	Multidisciplinary rehabilitation programs, physical therapy, exercise training, yoga
Walking difficulties	Dalfampridine	Assistive device, physical therapy
Numbness or Tingling	Numbness: none Tingling: gabapentin, pregabalin, carbamazepine, oxcarbamazepine, duloxetine, tricyclic antidepressants, Lidoderm patches, capsaicin cream	
Spasticity	Baclofen, tizanidine, dantrolene, clonazepam, gabapentin, levetiracetam, clonidine, intrathecal baclofen, cyclobenzaprine, methamethoxisole, methocarbamol, clonazepam, diazepam, isoniazid, clonidine	Botulinum toxin, physical therapy, exercise, transcranial magnetic stimulation, electromagnetic therapy, transcutaneous electrical nerve stimulation (TENS), cannabinoids
Muscle weakness	Dalfampridine	Exercise, assistive devices, medication, physical therapy, occupational therapy, Pilates training
Vision problems		Eye rest, special prisms
Dizziness or vertigo	Motion-sickness or anti-nausea drugs (e.g., meclizine, scopolamine, ondansetron), diazepam/other benzodiazepines	Vestibular therapy
Bladder problems	Onobatulinumtoxin A, desmopressin, tolterodine, oxybutynin, darifenacin, tamsulosin, terazosin, prazosin, propantheline, trospium	Intermittent catheterization, physical therapy, pelvic floor training, bladder stimulators

	chloride, imipramine, solifenacine succinate, capsaicin, myrbetriq, phenazopyridine, antibiotics (UTI prophylaxis)	
Sexual problems	Pro-erective medications (men), specifically: papaverine, vardenafil, alprostadil, sildenafil, tadalafil; filibanserin (women)	Vaginal lubricants (women)
Bowel problems	Docusate, bisacodyl, Metamucil, probiotics, magnesium citrate, magnesium hydroxide, Senna, Miralax, sodium phosphate, other enemas, glycerin, other suppositories, other laxatives	Dietary and lifestyle approaches
Pain	Gabapentin, pregabalin, carbamazepine, oxcarbamazepine, duloxetine, clonazepam, tricyclic antidepressants, lidoderm patches, capsaicin cream, low dose naltrexone	Cannabinoids, marijuana, massage therapy, acupuncture
Cognitive changes	Interferon, donepezil, galantamine, modafanil, amphetamines	Multidisciplinary rehabilitation programs, exercise training, behavioral training
Emotional changes		Physical therapy, exercise training, yoga, mindfulness-based interventions
Depression	Pharmacologic management as evaluated in non-MS populations, including older agents (e.g. MAO inhibitors, tricyclic agents), SSRIs, SNRIs, mood stabilizers (e.g. lamotrigine), specifically: venlafaxine, duloxetine, levomilnacipran, desvenlafaxine, olanzapine/fluoxetine, paroxetine, fluoxetine, bupropion, sertraline, citalopram, escitalopram, fluvoxamine, amitriptyline,	Psychotherapy, yoga, exercise training, acupuncture

	desipramine, nortriptyline, phenelzine, tranylcypromine, selegiline, isocarboxazid, mirtazepine, nefazodone, trazodone	

10.3 ABBREVIATIONS

AE	Adverse Event
AFT	Accelerated Failure Time
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DMT	Disease-Modifying Therapy
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Forms
ePRO	Electronic Patient-Reported Outcome
EDC	Electronic Data Collection
EDSS	Expanded Disability Status Scale
EDSS+	Expanded Disability Status Scale plus
FDA	Food and Drug Administration
GCIP	Ganglion Cell Inner Plexiform
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-To-Treat
JHCC	Johns Hopkins Coordinating Center
LCVA	Low Contrast Visual Acuity
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale
NCT	National Clinical Trial
Neuro-QoL	Quality of Life in Neurological Disorders
NMSS	National Multiple Sclerosis Society
NIH	National Institutes of Health

NINDS	National Institute of Neurological Disorders and Stroke
OCT	Optical Coherence Tomography
PASAT	Paced Auditory Serial Addition Test
PCORI	Patient-Centered Outcomes Research Institute
PDDS	Patient Determined Disease Steps
PH	Proportional Hazards
PI	Principal Investigator
PRO	Patient-Reported Outcome
QC	Quality Control
SAE	Serious Adverse Event
SDMT	Symbol Digit Modalities Test
SOA	Schedule of Activities
SOC	System Organ Class
TB	Tuberculosis
T25FWT	Timed 25 Foot Walk Test
UP	Unanticipated Problem
US	United States
9HPT	Nine Hole Peg Test

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.7	25APR2018	Added clinicaltrials.gov registration #, added diet and exercise questionnaires, clarified footnote to exclusion criterion, updated statistical analysis plan	Administrative changes and clarifications; collecting additional putative covariates that may be related to disability accumulation; increased power and efficiency in analysis of randomized clinical trials
1.8	23JUL2018	Described an optional biobanking substudy and made corrections to minor typographical errors. Clarification of one criterion for classification of high risk of longer-term disability.	Our overall goal is to identify biomarkers of long-term prognosis and treatment response in MS. An additional goal is to create a biorepository that can be leveraged for future studies; correction of typographical errors and clarification.
1.9	14MAY2019	Added funding source for biobanking substudy (NMSS), addition of EDSS exam, T25FWT and 9HPT to M18, M30 and M42 visits, clarification of MRI criteria for classification of risk of longer-term disability, addition of 2 new FDA-approved medications (cladribine and siponimod) to the protocol, clarification of how to handle enrollments in error (due to not meeting all inclusion/exclusion criteria), clarification of month 6 MRI timing for ascertaining breakthrough disease activity.	NMSS awarded funding to Johns Hopkins to support biobanking substudy; improvement in protocol that allows for each visit to contribute data toward primary endpoint definition; clarification needed since literature supports counting brain MRI lesions only; spinal cord lesions are captured under separate question and should not factor into count of T2 lesions; 2 new medications FDA-approved for RRMS; reasonable solution to un-randomize ineligible patients enrolled in error; SAC majority opinion on interpretation of MRI after 7 months on therapy.
2.0	10APR2020	Extended follow-up period by 9 months which allows for study participation of up to 63 months. Added Vumerity, Zeposia and generics for Gilenya to the list of first line (traditional) medications after SAC vote. The SAC agreed to automatically classify generics/biosimilars in the same group as the originally-approved medication in the future, with an option for raising concerns for a specific generic/biosimilar and handling by consensus voting if needed.	Extension of the follow-up period will help offset delays in recruitment and improve the power of the study to address the primary and secondary objectives. Vumerity, Zeposia and generics for Gilenya have been approved by the FDA and are available as treatment options for enrolled patients. Classification of other generics/biosimilars in the same group as the originally-approved

			medication makes sense clinically and scientifically.
2.1	16SEP2020	Added generic dimethyl fumarate to traditional medications, and added ofatumumab (Kesimpta) to the list of higher-efficacy medications, both after SAC vote and FDA approval. Prior exposure to ofatumumab is an exclusion criterion for study entry.	Ofatumumab (Kesimpta) has been approved by the FDA and is available as a treatment option for enrolled patients. Similar to other B-cell therapies, any treatment with ofatumumab in the past is an exclusion criterion. Generic dimethyl fumarate is now FDA-approved. The SAC previously voted to include it as a traditional therapy with the brand-name version, Tecfidera.

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