Protocol #:15-2388
Project Title: Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS)
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I. Hypotheses and Specific Aims:

Main hypothesis is that relatively older MS patients with no recent signs of new inflammatory disease activity (no relapses for at least five years and no new brain MRI lesions for at least three years) while on an approved MS DMT may safely discontinue DMTs from a medical perspective, ie no greater risk of new relapses or brain MRI scan changes due to MS, compared to those staying on their DMT. Secondary hypotheses are that in individual MS patients who discontinue DMTs in this context, there will be no significant increased risk of disease progression as measured by the EDSS, and no worsening of patient quality of life as measured by a series of Patient Reported Outcomes (PROs), compared to those staying on their DMT.

Specific Aims:

In MS patients 55 years of age or older, who have no evidence of new relapses for at least five years or brain MRI lesions for at least three years while continuously taking DMTs, we will compare clinically significant and patient-relevant outcomes in those who discontinue vs continue DMTs to determine if:

1. Risk of new relapses or brain MRI lesions is no worse in those discontinuing
2. Risk of disability progression (EDSS) is no worse in those discontinuing
3. Quality of life and other patient-reported outcomes (PROs) are no worse in those discontinuing

II. Background, Preliminary Studies, and Significance:

Multiple sclerosis (MS) is a debilitating neurologic disorder that is estimated to afflict over 400,000 and perhaps nearly 600,000 people in the US, and over 2 million worldwide[1]. At onset, it most often affects young people in the prime of their lives, with a median age of onset around 30.[2] The average lifespan is diminished by 7-14 years.[3-5] Most individuals with MS struggle with the condition for many decades. MS is a presumptive autoimmune condition affecting the central nervous system (CNS), including the brain, spinal cord and optic nerves.[6] Pathologically it is associated with demyelination, axonal loss and neurodegeneration of both the white and gray matter of the CNS.[6-8] On magnetic resonance imaging (MRI), lesions may similarly be seen in these locations. While formal diagnostic criteria have evolved over time, the concept of development and manifestation of CNS lesions disseminated in space (within the CNS) and over time, with other causes ruled out, remains the hallmark of MS diagnosis.[9]

MS is one of the most disabling conditions in the US and other Western countries. Patients, their families and society are affected with loss of neurological function, loss of employment, loss of social interaction, and high financial costs.[1,10-12] While a small percentage of MS patients have a relatively modest, or benign course, the vast majority of untreated MS patients develop measurable disability over time, with about half of untreated patients using a cane or other assistive device within 15 years of symptoms onset.[13] Those using a cane are about 75% likely to be unemployed due to MS and will endure annual medical costs about 10 times higher than those with no or minimal disability.[14]

Symptoms, especially early on in younger individuals, may relapse and partially or completely remit (relapsing-remitting MS, RRMS) in irregular patterns, often leaving decrements in neurological function as measured on the Extended Disability Status Scale (EDSS) or other scales. Relapses diminish significantly over time[15], and some individuals simply have no new relapses and stabilize neurologically. In the newest update of MS phenotypes, this is referred to as RRMS, inactive.[16] The majority, however, enter a phase of the illness dominated by slow progression of symptoms (secondary progressive MS, SPMS), with (SPMS, active) or without (SPMS, inactive) superimposed relapses or new MRI lesions. Some individuals never have overt RRMS, but simply have slow progression from the outset (primary progressive MS, PPMS).[16] Progression may also be ongoing (SPMS or PPMS, progressing) or not ongoing (SPMS or PPMS, not progressing).[16] Median age of onset of progressive symptoms, either SPMS or PPMS, is about 40,[17] and other risk factors for development of SPMS include male sex, older age at onset, and frequent relapses early in their course.[18-20] Notably, relapses occurring later in the disease course, especially those after the onset of SPMS, have little or no impact on accumulation of disability.[21] In addition, with the advent and development of MRI scans over time, many individuals have been identified who may have had a single relapse and fulfill some, but not all, MS diagnostic criteria, but have substantial risk of further disease activity, so-called clinically isolated syndrome (CIS).[22] Finally, a small minority of individuals have undergone brain MRI scans for symptoms seemingly unrelated to MS, yet,

upon review, have MRI abnormalities highly suggestive of demyelination and MS, so-called radiologically isolated syndrome (RIS). Preliminary studies suggest these individuals also are at high risk of developing clinical syndromes consistent with MS.[23]

MS symptoms and disability result from a combination of CNS inflammation and neurodegeneration over time.[6] Inflammation is most prominent early in the course of the disease, especially in young adults with RRMS, but wanes over time, as measured by decreasing acute relapses,[10] decreased gadolinium-enhancing lesions on magnetic resonance imaging (MRI),[24] and as shown on pathological analysis at autopsy.[7] SPMS and PPMS, with older age of onset, are associated with fewer (or no) relapses; less active, inflammatory MRI lesions; and less pathological evidence of acute inflammation.[7] Thus, the disease course can be conceptualized as consisting of two (overlapping) phases: the early, inflammatory phase with relapses, new lesions on MRI, and early neurodegeneration, and a later phase dominated by neurodegeneration, with slow disease progression and no overt signs of inflammatory activity for many. While there remains substantial disagreement as to whether MS represents one or more disease conditions, the most parsimonious conclusion is that MS represents a single disease entity with varying manifestations related to the aging process. As noted by Confavreux and Vukusic, [17] "These observational data on the natural history of multiple sclerosis suggest that the clinical phenotype and course of multiple sclerosis are age dependent. Relapsing–remitting disease can be regarded as multiple sclerosis in which insufficient time has elapsed for the conversion to secondary progression; secondary progressive forms as relapsing–remitting multiple sclerosis that has 'grown older'; and progressive from onset disease as multiple sclerosis 'amputated' from the usual preceding relapsing–remitting phase."

Treatment of MS falls into several broad categories. Individuals with MS may potentially reduce the likelihood of further disease activity with exercise, not smoking, using a low salt diet and maintaining adequate vitamin D levels.[25] Severity and duration of acute relapses may be minimized after onset with brief courses of high-dose corticosteroids.[26] Many symptoms may be relieved with a variety of approaches including behavioral changes; physical, occupational and speech therapy; medications; and use of assistive or implantable devices. Controlling co-morbidities is also important.[27] In addition, there are now ten separate molecules and 14 formulations/doses of medications approved in the US by the FDA that alter the natural history of the disease, so-called disease modifying therapies (DMTs). The MS DMTs have been shown to reduce relapses (annual relapse rate, time to first relapse); decrease development of new MRI lesions (T2/FLAIR, T1 gadolinium-enhancing lesions, T1 "dark holes", atrophy measures and many others); and slow progression of disability (as measured on the EDSS and other scales) over relatively short periods of time, with most Phase III studies being two years in length (please see reference 28 for an exhaustive review of the presently available MS DMTs).

All FDA-approved MS DMTs alter or suppress the immune system, and are effective in RRMS, but the only PPMS or SPMS patients who appear to benefit are younger (typically under about 50 years), have had a recent acute relapse in addition to their slow progression, or have gadolinium-enhancing lesions on MRI scans.[29-31] Thus, the MS DMTs are considered to be anti-inflammatory by nature, and have no known effects on enhancing or stimulating CNS repair, i.e. they do not appear to help improve neurological function in those with fixed disability. While highest patient preferences for attributes of MS DMTs might be for medications that would improve symptoms,[32] with the exception of natalizumab[33,34] and dimethyl fumarate,[35] MS DMTs have not been proven to have positive effects in reducing the ongoing MS symptoms or improving quality of life in MS patients. In addition, MS DMTs have a wide range of potentially significant short-term tolerance issues and long-term side effects that limit their use in many patients (see reference 28). Studies supporting the use of DMTs in relapsing MS have median participant ages of 32-38 years, but the negative trials in SPMS or PPMS studies usually enroll those with a mean age of 45 years and above. Most DMT trials in all MS subtypes exclude those over the age of 55, presumably to limit the effects of confounding co-morbidities which increase with age. Few long-term treatment studies have been performed, and none have employed untreated control groups for extended periods such as five years or longer. As a result, it is unclear how long MS DMTs are needed or remain beneficial from either the researcher/doctor's point of view, or that of the patient. As noted by Tremlett, et al, [15] "First, any drug that is able to modify relapse rates has the greatest potential for a population impact in those aged <40 years and within the first demi-decades of disease when the risk of a future relapse is at or approaching its peak. Second, continuation of a relapse-modifying drug much beyond these periods may result in the risk of adverse effects from drug treatment, outweighing any possible benefits."

Significant attempts have been made to understand the patient's perspective with regard to both initiation and discontinuation of MS DMTs. While shared decision-making is the norm for both initiation and discontinuation of MS DMTs, patients more commonly note it is primarily their decision when discontinuing MS DMTs.[36,37] In spite of documented benefits of the MS DMTS, patients continue to display high discontinuation and low adherence rates. Reasons for discontinuation include: side effects, perceived lack of efficacy, costs, pregnancy, not wanting to be reminded about having MS, and perception that risk outweighs the benefits.[36-54] Perception of risk may vary by age, sex, duration of disease and degree of disability, and risk may be assigned to both the disease itself, as well as the methods used to treat it. We are unaware of any study that explicitly examines the attitudes of individuals with MS who have been stable from the point of view of new inflammatory disease activity (i.e. "the medication is working"), and asks them to consider discontinuing their DMT. It has been our personal experience that individuals with MS might fall into

several categories in this context. Some link the absence of new relapses and MRI changes directly to the use of the MS DMT, and they are willing to put up with the inconvenience, cost and side effects of the medication in order to maintain this status. Patients frequently describe continued use as an insurance policy or security blanket. This is likely truer for those with benign, or inactive, RRMS, and minimal side effects or costs. On the other hand, many individuals with MS have been taking DMTs for many years, some persisting in spite of significant side effects, and they are very willing to consider a DMT discontinuation trial. For them, the combination of inconvenience, side effects and costs of the DMTs, in conjunction with the perception that the medication may no longer be necessary or effective as they age, marks discontinuation as an attractive option. This might be truer for those with significant side effects of the DMTs, or those with progressive forms of MS, (i.e. they have had no new relapses or MRI changes, yet they continue to worsen). For either RRMS or progressive forms of MS, the ultimate fear when considering a trial of discontinuation is that they may undergo a negative change in their functional status, as manifested by either a severe, disabling relapse, or an acceleration of underlying progression of disability.

Finally, the costs associated with the use of MS DMTs have skyrocketed over the 21+ years since the original approval of interferon β-1b in 1993. Based on 2013 prices, the average cost of both the newer and older DMTs is about $60,000 per year.[55] This does not include costs related to medical office visits for monitoring, the monitoring costs themselves (e.g. laboratory studies), lost time at work, infusion costs (for natalizumab, alemtuzumab and mitoxantrone), or the extra costs incurred when drug-related side effects develop and need to be managed with other interventions (e.g. treating infections). Seven of the 80 most costly drugs in the US in 2014 were MS DMTs, [56] accounting for expenditures over $11 billion. At $60,000 per year, 100 patients aged 55 would collectively spend $60,000,000 if they continued to use a MS DMT over a decade until age 65. While medical insurance has covered a great deal of the financial burden, representing a large societal burden, many of these costs are borne by the patient and their family as well. Of course, if the medications are beneficial, and result in costs savings due to less disability and related issues (e.g. unemployment due to MS), these costs may be justifiable. The use of simulation models and outcome measures such as the quality-adjusted life year has allowed for cost-effectiveness comparisons between the various DMTs[57]. But if at some point and/or some age there is minimal benefit, or an overall detrimental effect on neurological/other function with continuation of MS DMTs, it would be difficult to justify their ongoing use.

As with many chronic conditions which may wax and wane over time, the duration of time when the MS DMTs continue to offer benefits that outweighs the risks and costs of use remains unclear. Development of antibodies against the DMT,[58,59] or ongoing disease activity, as measured by continued relapses, accumulation of MRI lesions or worsening disability, may signal that continued use of that one agent is futile. Otherwise, there are no specific radiological, serological, biochemical or other biomarker to guide decisions about continuing present therapy, switching to an alternative, or considering a discontinuation trial. Discontinuation of MS DMTs, however, has led to recurrence of significant disease activity starting between 4-28 weeks after DMT cessation in younger patients (between ages 29-50).[60-65] In these studies, reasons for discontinuation included removal of natalizumab from the market after the unexpected development of the serious brain infection, progressive multifocal leukoencephalopathy (PML); deliberate attempts to reduce risk of PML with “drug holidays”; state-mediated discontinuation of insurance coverage (interferons in Poland and Finland); or simply to determine the nature, degree, and timing of disease recurrence (small early interferon studies assessing return of gadolinium-enhancing lesions on MRI). The resurgence in disease activity after discontinuation was compared with disease activity of the patients prior to discontinuation, or to activity within previously compared placebo controls, but none of these studies were randomized, controlled discontinuation trials. None explicitly studied DMT discontinuation in relatively older individuals with no new relapses or MRI lesions for a protracted time, i.e. appear to be at lower risk of new inflammatory disease activity that would potentially benefit from an anti-inflammatory medication. For comparison, in a recently reported randomized discontinuation trial[66] of medications in early, active rheumatoid arthritis, among individuals (mean age 50) successfully treated with etanercept and methotrexate for 52 weeks, a majority of individuals transitioned to placebo developed significant disease recurrence after a further 65 weeks of monitoring.

With regard to potential benefits of MS DMT discontinuation (especially using Patient Reported Outcome measures –PROs) it is possible patients may appreciate less side effects, inconvenience and costs after discontinuation. Use of natalizumab, however, has been associated with improvements in quality of life measures[33,34] while in use, and discontinuation has been associated with worsened cognitive function in a recent study.[67] It also has been our anecdotal experience that discontinuation of natalizumab frequently results in diminished quality of life, especially in younger patients. Thus, discontinuation of MS DMTs may be associated with better, or worse, symptomatic control as perceived by patients.

Two studies have reported data relevant to discontinuation of DMTs in relatively older MS patients with no recent new inflammatory disease activity. One is a prospective, unblinded, observational analysis[68] of 182 MS patients enrolled in the international MSBase Registry who were over 40 years old and relapse- and disability progression- free for at least 5 years at the time when they discontinued their DMTs. Reasons for discontinuation were varied, and included perceived lack of efficacy, inconvenience, and side effects. The cohort was followed for at least 3 years after DMT was stopped (median - 4.2 years, range 3 - 14.7 years). During the follow up period, clinician-recorded relapses

were observed in 24.2% of patients, sustained 3-months disability progression in 31.9%, and 10.6% experienced both relapses and disability progression. Higher baseline disability score (EDSS) predicted lower risk of relapses, in line with the observations that the more disabled patients in the later stages of the disease have decreased relapse rates.[15] Importantly, although the total number of relapses in this cohort during the observation period exceeded 80, only 7 relapses were seen in 38 patients over 55 years of age or an approximate 5% risk per year. The same group of investigators have carried out additional analysis wherein older, stable MSBase patients who stopped DMTs were propensity-matched to patients who continued on a DMT. The authors did not observe increased rates of relapses or disability in the group of 'DMT stoppers' (Kister I et al, manuscript in preparation), which further bolsters the rationale for conducting a formal randomized DMT discontinuation trial as proposed here.

A second[69] unblinded, uncontrolled, observational study looked prospectively at individuals with MS who were older and considered stable (no new relapse or brain MRI lesion) for 8-10 years while on a DMT, and who deliberately discontinued their DMT to see if they would remain stable by that definition. Over three years, 94% who agreed to discontinue their DMT (there was no information available on those who did not enter the study and presumably stayed on their DMT) had no new relapse or brain MRI lesion after discontinuation of MS DMTs. Both RRMS and SPMS were included, however measures of disability were not assessed. The greatest factor that predicted recurrence of inflammatory disease activity was younger age, with mean age of those recurring vs non-recurring being 53 and 62, respectively. In neither of these studies were PROs reported.

Potential discontinuation of DMTs in MS has been the subject of an Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review (Number 150)[70] in the spring of 2015. It found that, "Evidence was insufficient for long-term benefits of DMTs for secondary progressive MS patients and most outcomes for relapsing-remitting MS (RRMS) patients." It also noted, "No literature directly compared continuing vs discontinuing DMT in comparable populations." Ultimately, the authors concluded, "MS patients and providers have little information to guide decisions to discontinue DMT." The thrust of the document was that virtually no studies of use of MS DMTs have been long enough to prove that prolonged use of these medications results in benefits that outweigh their potential risks and side effects. It also reviewed the literature on patient perspectives on the use and discontinuation of MS DMTs, noting patients and providers struggle to develop specific algorithms to define when a personal discontinuation trial may be warranted, feasible and safe. In this context, personal preferences about risks take on greater weight.

Thus, a significant information gap exists about a condition that is both significantly debilitating to patients, and costly to those afflicted with MS and to society. There may be both risks and benefits to the patient when continuing *or* discontinuing MS DMTs, and patients may view risks and benefits quite differently from their physician. It appears the MS population that has the lowest risk, and perhaps is most likely to benefit, from potential discontinuation of MS DMTs, is relatively older patients with no recent evidence of new inflammatory disease activity. We propose to study deliberate discontinuation in this subpopulation of MS patients, to determine if DMT discontinuation is safe and results in no worse physician-derived and patient-reported outcomes.

With regard to preferential attributes of MS DMTs, in a recent study[32] MS patients identified the highest preference for medications that improve MS symptoms, an outcome not typically seen in MS treatment trials or in practice (with the exception of natalizumab[33,34]). Prevention of new MRI lesions or disease symptom progression were also important, while prevention of relapses was not highly rated. Thus, while we will use the outcomes in AIM#1 to assess safety as it relates to new inflammatory disease activity, we are extremely interested in patients' perceptions of their symptoms and quality of life. The main symptoms are trouble with walking and balance; fatigue; cognitive impairment; mood impairment; bowel, bladder and sexual dysfunction; pain; stiffness or spasticity; and incoordination. Many psychosocial functions include independence in activities of daily living (ADLs); employment; and engagement in social activities such as family and religious interactions.

The patient viewpoint is central to decision-making when considering discontinuation of a MS DMT, and might be based on a variety of factors that have more to do with daily symptoms and quality of life, and less to do with potential and theoretical long-term benefits, such as less new relapses and brain MRI lesions. Important symptoms will be assessed with the PROs we have chosen so far. We will also assess the potential role of side effects in decision-making, comparing these at baseline and over time. Our study design will allow us to compare a series of patient-centered outcomes focused on a broad array of symptoms and functions in those discontinuing vs continuing MS DMTs. While many MS patients recognize the importance of the relapse, EDSS and MRI activity, it will also be extremely important to ascertain the relative levels of importance of these physician-derived measures compared to the PROs. That is, it is possible study participants will accept trade-offs that favor one outcome or set of outcomes compared to another. For example, a patient may be willing to accept a small change on a brain MRI scan, if they no longer have side effects of a DMT, or have significantly increased disposable income due to elimination of drug and related costs. The patients themselves will be indispensable in trying to understand how these trade-offs might be contemplated and acted upon.

This is a pragmatic clinical trial, based on real world patterns of patient decision-making. As such, all of the study visits will be attached to routine office visits, and the patient/their insurance will be responsible for payment of standard

of care aspects related to the study. This will include a baseline brain MRI, as well as annual brain MRI scans at year one and year two, and all routine safety monitoring as would be obtained in a typical office setting for that individual medication. The funding agency, the Patient Centered Outcome Research Institute (PCORI), will be responsible for all research aspects, including data acquisition and manipulation, performance of a 6-month "safety" brain MRI (which is NOT standard of care), all research personnel, and all regulatory review. In addition, while this is a randomized discontinuation trial, all patients will be aware of their medication assignment, but observers of the main outcomes (relapses, MRI changes and the EDSS) will be blinded.

III. Research Methods

A. Outcome Measure(s):

a. **Specific Aim 1:** The primary outcome being measured is safety, i.e. is there a significantly increased risk of inflammatory disease activity, as manifested by either a new MS relapse (Protocol defined, see below) and/or a new brain MRI lesion, in those who discontinue MS DMTs vs those who continue. We have specifically chosen inflammatory markers of disease activity because that is what the MS DMTs have been shown to have an impact on. As inflammatory disease activity may be manifested clinically as a relapse, or radiographically as a new MRI lesion, we have chosen a combined primary outcome measure. In addition, it is a measure which will record the mildest manifestations of new inflammatory activity, i.e. should be a sensitive marker, which is important for a safety investigation.

b. **Specific Aim 2:** The EDSS is a commonly used assessment that allows clinicians to objectively measure changes in a patient's symptoms by using unbiased raters.[81, 82] This assessment will be collected at all time points and will be used to measure changes in patients symptoms over the course of the study and will be used to help define 'relapse', i.e. will require a change on examination. The measure used in this study will be based on the Kurtzke Functional System Scoring (FSS)/EDSS.

c. **Specific Aim 3:** The PROs being collected in this project are;

i. **Neuro-QoL (quality of life) short form**: The Neuro-QOL Adult PRO short form measures are self-reported measures of overall quality of life and functioning relevant to and tested in patients with a variety of neurological conditions including MS since its introduction in 2011.[76] This measurement system, sponsored by the National Institute of Neurological Disorders and Stroke, is the newest PRO measurement system. It encompasses several domains including physical, emotional, social, and cognitive functions.[33] These scales are developed to assess health-related quality of life (HRQOL) and are developed to collect quality of life in patients with various Neurological disorders. This allows for future research where we can compare quality of life responses in this MS population as compared to other patients in the same age range with other neurological disorders. The Neuro-QOL short form represents a superior measurement system compared to the existing MS-specific PROs, as it is based on the newer item response theory (IRT) rather than the older classical test theory (CTT).[77] IRT has a number of advantages over CTT methods. Primarily, CTT models assume that measurement error is distributed normally and equally for all score levels.[78] In IRT, measures of precision are estimated separately for each score level or response pattern, controlling for the characteristics (e.g., difficulty) of the items in the scale. From these domains, the following item banks will be utilized: Physical Domains (Upper Extremity Function, Lower Extremity Function- Mobility), Symptom Domains (Fatigue, Sleep Disturbance), Mental Domains, Cognitive Domains (Applied Cognition- General Concerns, Applied Cognition- Executive Function, Communication),Emotional Domains (Anxiety, Depression, Positive Affect and Well-Being, Emotional-Behavioral Dyscontrol), Social Domains (Satisfaction with Social Roles and Activities, Ability to participate in social roles and activities). The Neuro-Qol short form scales consist of single scale item scales. Since we propose to use the static (i.e., each patient receives the same set of questions) short forms of each of these measures, most scales comprise 8 items and can be administered online or on paper, with a completion time of 1-2 minutes.

ii. **SymptoMScreen (SymptoMScreen – overall symptom severity):** SymptoMScreen[79] is a rapid assessment tool that allows the patient to self-report across multiple neurological domains (mobility, hand function, spasticity, pain, sensory, bladder, fatigue, vision, dizziness, cognition, depression, and anxiety). This scale is a user friendly, single page validated measure that allows for quick assessment of multiple symptoms.

iii. **Patient Determined Disease Steps (PDDS – disability)**: The Patient-Determined Disease Steps (PDDS) is a PRO version of the clinician-reported Extended Disability Status Scale (EDSS) which hones the stages of cane use and thus is more responsive to mid-range disability changes.[79] This tool asks the patient to characterize level of disability into one of nine steps (0=normal, 1=mild disability, 2=moderate disability, 3=gait disability, 4=early cane, 5=late cane, 6=bilateral support, 7=wheelchair scooter, 8=bedridden). The PDDS will be used to characterize (and to control for) disability in both study groups at all study time points.

iv. **The Symbol Digit Modalities Test (SDMT - cognition):** The SDMT measures patient attention, concentration, and speed of information processing and has been validated for discriminating patients from

controls even when it was administered each month over six months.[83] It is relatively simple to administer and only takes a few minutes to complete.

v. **Multiple Sclerosis Impact Scale (MSIS-29 – MS symptoms**): Since Neuro-QoL short form doesn't have the ability to provide an overall quality of life calculation, the study team added MSIS-29, which is an acceptable, reliable, and valid method for recording quality of life in MS patients.[80]

vi. **Treatment Satisfaction Questions:** This was developed for qualitative and exploratory purposes. These questions will provide insight into patient satisfaction in regards to the disease modifying therapy (DMT) they are using at baseline, versus their ongoing satisfaction with their study care plan (on a DMT v. not on a DMT). The following question will be asked:

How satisfied are you with your current DMT (or lack of DMT)? Please circle one.

Very dissatisfied Dissatisfied Neutral Satisfied Very satisfied

vii. **Treatment Decision Questions**: These question was also developed for exploratory purposes to gain insight on the MS DMT treatment decisions at the conclusion of the study and to better understand recruitment and retention, for patients who were randomized to either staying on or going off their DMT. The following question will be asked:

What do you plan to do for your MS medication after completing the study? Please circle one.

If you are in the continue group:

Stop my DMT Continue my current DMT Switch to a new DMT

If you are in the discontinue group:

Stay off of my DMT Re-start a prior DMT Re-start a new DMT

What is the main reason you participated in the DISCOMS study? Please circle one.

a) To possibly stop my MS medication, b) Increased access to doctor, nurse, and study team, c) Increased monitoring of my disease, ex. more frequent MRI, d) Possibility of saving money by going off my MS medication, e) Participation in clinical research to further medical knowledge of MS, f) Other: Please list other reason(s)

What is the main reason you stayed in the study? Please circle one.

a) To possibly stop my MS medication, b) Increased access to doctor, nurse, and study team, c) Increased monitoring of my disease, ex. more frequent MRI, d) Participation in clinical research to further medical knowledge of MS, e) Other: Please list other reason(s)

B. Description of Population to be Enrolled:

Inclusion criteria:

- RRMS, SPMS, or PPMS by McDonald 2010 criteria[9]. Patients will be defined by subtype based on 2013 updated phenotypic criteria[16]. Progression of MS will be defined by the local principal investigator either prospectively with an EDSS change of at least 1.0 points over the last two years, or retrospectively, with any significant change in motor function over at least one year, unrelated to relapse.
- 55 years of age or older at time of randomization;
- No evidence of recent new inflammatory disease activity (inactive by the Lublin criteria[16]) with no new relapse for at least five years and no new MRI lesion for at least three years
- Using any of the FDA-approved MS DMTs (to include interferon β-1a, interferon β-1b, glatiramer acetate, natalizumab, fingolimod, dimethyl fumarate, ocrelizumab, or teriflunomide; see exclusions below) continuously* for no less than 5 years.
- Taking most recent DMT continuously* for no less than two years.
- Willing to be randomized per this protocol; each patient will be questioned as to their willingness to stay in the trial regardless of the group to which group they are randomized.
- Willing to follow the protocol
- Able to undergo a brain MRI without anesthesia

* Continuously will be defined as no less than 75% of all prescribed doses, with no time of greater than four weeks from last intended dose to have missed a dose (8 weeks for natalizumab, i.e. one missed dose).

Exclusion criteria:

- Any MS relapse in the last five years, as determined at the screen visit by the PI
- Any new or definitely enlarging T2/FLAIR lesion or new gadolinium-enhancing lesion within the past three years (at least two scans separated by at least three years must be reviewed, with the most recent scan being no more than 6 months prior to randomization) on brain or spine MRI scan. Lesions must be 3mm or larger to be exclusionary.
- Significant (as defined by the PI) intolerance of presently-used DMT
- Use of any non-FDA-approved DMT in the last 5 years.

- More than two courses of acute, systemic (IV or oral) steroids in the last 5 years or any use within the last year. Course is defined as three or more days continuously, and not to exceed 14 days. No use of chronic, systemic steroids, defined as 15 or more days, in the last 5 years. Any use of steroids to treat MS relapse, possible relapse, or pseudo-relapse in the last 5 years. Inhaled or topical steroids are not exclusionary.
- Prior use of alemtuzumab, mitoxantrone, cyclophosphamide, methotrexate, cyclosporine, rituximab, siponimod, or cladribine in the last 5 years
- Prior use of any experimental agent used as a DMT for MS in the last five years
- Other significant medical or psychiatric illness, if uncontrolled. Examples: uncontrolled hypertension, uncontrolled diabetes, uncontrolled asthma, uncontrolled depression
- Cancers other than basal cell skin cancers within the last 5 years
- Unable to give informed consent or follow the protocol
- Unable to undergo brain MRI
- Unwilling to be randomized per this protocol
- History of other chronic neurological illnesses that might mimic MS with chronic or intermittent symptoms (i.e. ALS, myasthenia gravis, chronic neuropathy, etc.)

C. Study Design and Research Methods

This will be a randomized discontinuation trial (RDT).[71] While RDTs have been done in cancer[72,73] and rheumatoid arthritis patients,[66] this would be the first such study in MS. Patients will be randomized to either continue with their present MS DMT (control), or discontinue their present DMT (experimental), in a 1:1 fashion using the Interactive Voice Response System (IVRS) randomization system. A total of up to 265 patients will be consented and enter the trial. After allowing for up to 15% dropout rate, we aim for 225 (112 in each group) patients to complete the study. Patients enrolled after July 31, 2019 will not complete the full two years of assessments; study follow up will only continue until September 1, 2021. There will be no placebo, and no sham treatment. There will be no taper period. (Please see the statistics sections for power analyses).

At each site, extensive chart review will be used to identify eligible patients. Patients will be approached at their next standard of care clinical visit by their primary neurologist and/or a study coordinator about participating in the study. Either the patient's primary neurologist or the study PI will verify inclusion/exclusion criteria and ensure that all patient's questions are answered before consent is signed. Study information may be distributed in the community in order to recruit participants from other sources. Patients who do not receive their standard neurological care at the study site will be encouraged to transfer their neurological care to the study site for the duration of the study. If this is not possible, these subjects must agree to have standard of care MRIs done by their primary neurologist yearly throughout the study and have the results sent to the study site. MRIs at the 6-month time point must be conducted at the study site. All research visits will be conducted at the same time as SOC visits when possible, or as separate visits if not possible.

Please see Table 1 below for the schedule of study activities.

Table 1: Schedule of Research Assessments

MS Patients consented for the study	T_0 (Baseline)	T_1 (6 Months +/- 1 week)	T_2 (12 Months +/- 1 week)	T_3 (18 Months +/- 1 week)	T_4 (24 Months +/- 1 week)***	Unscheduled Visit*	Phone follow-up (monthly +/- 1 week)
Informed Consent	X	-	-	-	-	-	
Inclusion/Exclusion	X	-	-	-	-	-	
Physical Exam/ MS Medical History	X	-	-	-	-	-	
Vitals	X	X	X	X	X	X	
Prior/Con Meds	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Comorbidities	X	X	X	X	X	X	
Neuro-QoL Short Form	X	-	-	****	X	X	
PDDS	X	X	X	X	X	X	
SymptoMScreen	X	X	X	X	X	X	
MSIS-29	X	X	X	X	X	X	
SDMT	X	X	X	X	X	X	
Treatment Satisfaction Question	X	X	X	X	X	X	
Relapse Assessment	X	X	X	X	X	X	
EDSS (by unbiased Rater)	X	X	X	X	X	X	
Treatment Decision Questions	-	-	-	****	X	X	
MRI**	X	X	X	****	X	-	

*Unscheduled visits may occur for patients during the study. If an MRI is requested by the PI in relation to an unscheduled visit, that MRI would be paid through standard of care.
**T_0, T_2, and T_4 MRIs paid as part of standard of care (SOC). T_1 MRI paid as research only and must be performed at the study site. T_0 Brain MRI to be performed within 6 months preceding study entry, and will be reviewed and confirmed as fulfilling entry criteria. If T_0 MRI results for a potential subject from within the last 6 months are not available, the patient should be scheduled for a Standard of Care MRI and these results should be reviewed for inclusion/exclusion criteria prior to enrollment into the study and completion of Baseline visit.
***Participants enrolled after July 31, 2019 may not complete T_4, but will be followed until September 1, 2021. If T_3 is on or before June 30, 2021, participant should come in for an out of window T_4 visit before Sept. 1, 2021.
****If T_3 falls after June 30, 2021, participants will not come in for a T_4 visit, but will complete a NeuroQoL and Treatment Decision Question during T_3, and will have an out of window Month 24 MRI.

After thorough discussion of the trial and signing an informed consent, participants will be seen at five specified time points: T_0, screen/baseline; T_1 at 6 months; T_2 at 12 months; T_3 at 18 months; and T_4 at 24 months. Patients will be screened, have a baseline brain MRI reviewed, undergo a relapse assessment and EDSS exam, complete all PROs, and be randomized at T_0. They will be examined every 6 months at times T_0, T_1, T_2, T_3, and T_4 and undergo MRI scans of the brain at times T_0, T_1, T_2, and T_4. If T_3 occurs after June 30, 2021, participants will not be seen for a T_4 visit and they will complete the NeuroQoL and Treatment Decision Question during T_3. If the T_3 visit occurs on or before June 30, 2021, the patient will be brought back in for a T_4 visit prior to September 1, 2021. Patients who have finished the study prior to protocol v. 10Jan2020 approval will be contacted via phone to obtain verbal consent, and will then be asked the Treatment Decision Question.

All DMTs will be treated as a single group, as the analysis is not powered to ensure an effective subgroup analysis by DMT type. With an assumption of 225 finishing participants, this will allow an attempt at subgroup analysis by DMT, sex, age epochs, disease duration, and others. To study each DMT independently would require large, impractical numbers of participants. All research visits will include a formal relapse assessment by the Examining Physician (EDSS rater) in conjunction with the PI (see section E).The baseline/screening T_0 MRI will have been obtained no more than 6 months prior to randomization. All study MRIs may be obtained on the MRI machine at the enrolling site or any other site, so long as obtained with a 1.5 tesla or stronger magnet. Prior to enrollment, the enrolling physician will certify, based on their personal review of the prior scans and/or reports, that the scans have been stable for a minimum of three years (review of minimum of two scans, although it could be more, separated by at least three years). MRI scans at 12 and 24 months will be performed as per usual SOC, paid for by patient insurance, at whatever site is normally used by the patient (preferably the same scanner each time, and preferably the same scanner as the investigation site), and should be done with and without contrast. Gadolinium may be withheld at the discretion of the PI. The 6 month T_1 MRI should be performed at the enrolling site using a standardized protocol to include gadolinium, and this scan is considered to NOT be part of SOC, and is paid for by the study funder. All T_1, T_2, and T_4 month MRIs will be obtained within 30 day of the study visit (either before or after), and analyzed by a central, board-certified, blinded neuro-radiologist for new activity compared to prior scans. If T_4 MRI falls out of this 30 day window, i.e. because of insurance coverage), the MRI information may be collected up to 6 months after the visit.

Patients will overall be randomized in a 1:1 fashion to either continue or discontinue their present DMT. They will be randomized within each site to either the continuation or discontinuation group in blocks of 2, 4 or 6 through simple random sampling. Patients with all forms of MS, RRMS, SPMS and PPMS will be offered participation, and because patients with all forms of progressive disease tend to act in a similar manner with regard to ongoing disease activity, SPMS and PPMS will be merged into a single category, progressive patients, for any subanalysis. Patients within each category, either relapsing or progressive, will also be randomized in a 1:1 fashion to continue or discontinue their DMT, but we will not stratify a certain number of either category of patients for overall participation. All MRI scans will be read locally for safety and clinical purposes, and PIs will communicate any significant MS or non-MS findings to the primary neurologist (should they not be the primary neurologist). Any new lesion documented on the T_1 or T_2 MRI scan will prompt delivery of a notice within 48 hours, to the PI, that the patient has achieved the endpoint of the study, with a description of relevant findings.

In the event of a suspected relapse, the patient will be instructed to contact their physician and the study coordinator at their local site within 48 hours of new symptoms, and come in for an unscheduled visit and relapse evaluation within seven days of symptom onset. Use of corticosteroids will be at the discretion of the patient and the local PI or other physician. Use of systemic steroids to treat MS symptoms will be concluded to be a Protocol defined relapse. As at scheduled visits, the determination of a relapse at an unscheduled visit will be made by the blinded EDSS examiner, who will perform the EDSS and only then receive information about recent clinical history.

D. Risks/Safety:

A Data Safety Monitoring Board (DSMB consisting of three board-certified neurologists not otherwise associated with the study and biostatistician) will be employed to perform twice yearly reviews of the data and certify that it is acceptable for the study to continue. It is possible that, in spite of a prolonged period with no new inflammatory disease activity, those who discontinue their DMTs will have a substantial increase in inflammatory disease activity, or progressive disease

based on EDSS, or worsened patient quality of life, compared to continuers. This could be especially important for those discontinuing natalizumab, where there remains significant concern, and also disagreement, about the potential for not just recurrence of disease activity, but also significant rebound (ie, higher than prior baseline) of disease activity.[63-65,70] As such, we will perform interim analyses at two pre-specified time points, when 25 (Tables 2, 4 below) and 65 (Tables 3, 5 below) patients in each group have completed their six-month evaluation or achieved the primary endpoint, ie if a participant has an acute relapse at any time, including before the T_1, 6 month safety check, or is noted to have a new or enlarging T2 brain MRI lesion, they will be considered to have achieved the primary endpoint. We would require the DSMB to consider discontinuing the study if either of the following occurred at either interim analysis time point:

- The difference in the proportion of events between the discontinue and continue groups was statistically significantly (alpha = 0.025) greater than 0.10. Presumably the discontinue group would be greater.
- If one group, presumably the discontinue group, had an event proportion statistically significantly (alpha = 0.025) greater than the expected number of cases defined by the continue group.

Primary endpoints will be defined as either:

1. "Relapse" will be defined as the appearance of new neurological symptoms or worsening of pre- existing neurological symptoms lasting at least 48 hours in a subject who had been neurologically stable or improving in the previous 30 days *and* accompanied by objective change in the neurological examination corresponding to that symptom (worsening of 0.5 point on the EDSS or worsening by 1.0 or more points on the pyramidal, cerebellar, brainstem or visual functional system score). Fatigue or subjective cognitive worsening, alone or in combination, will not be considered a "Protocol defined relapse."

Each Relapse event will be categorized on CRFs as one of the below:

- **Protocol defined relapse**

  A relapse seen within 7 days of onset, independently and blindly observed as a change in EDSS by the Examining Clinician. This relapse is defined as: the appearance of a new symptom or worsening of an old symptom, attributable to MS; accompanied by a change in the neurologic examination attributed to those symptoms (defined as worsening of 0.5 point on the EDSS or worsening by 1.0 or more points on the pyramidal, cerebellar, brainstem or visual functional system scores); symptoms lasting at least 48 hours in the absence of fever; and preceded by stability or improvement for at least 30 days. Any use of systemic steroids to treat MS symptoms will be counted as a Protocol defined relapse, regardless of when the patient was seen.

- **Out of window relapse**

  Same as a protocol defined relapse, except that the patient was not seen within the 7-day window.

- **Suspected relapse**

  Relapse that fails to meet the above situations, but may have been a relapse –i.e. all circumstances point to a relapse, but upon examination by the examining physician, no residual or change in the EDSS is noted.

- **Not a Relapse**

  Pseudo-relapse, ie a worsening of pre-existing neurological symptoms in the context of any significant stressor, including, but not limited to, infection, or physical, psychological or mental stress, as determined by the treating physician; or other symptoms felt not to be related to MS

For the primary outcome, we will use Protocol defined relapse for analysis, with secondary analyses combining this with Out of window and Suspected relapses. For the above categorization, it is imperative that the subject be seen at time of relapse. Once the patient feels that they have experienced a relapse, the patient needs to contact the PI and study coordinator as soon as possible. Patients need to be seen at the clinic ideally within 1-3 days, and within 7 days at the latest, of onset of symptoms or the relapse will not qualify as a Protocol defined relapse. If the patient is unable to identify whether he/she is experiencing a relapse and does not contact the clinic to be seen within 7 days, it does not qualify as a Protocol defined relapse. When subjects are not scheduled for a clinic visit, the coordinators will call them on a monthly basis to assess potential relapses. The purpose of this phone call is to determine whether the patient is experiencing a relapse, or has experienced a relapse since the last clinic visit or phone call. As with scheduled visits, at an unscheduled visit the Examining Clinician will determine if a relapse occurred based on the EDSS evaluation, and a post-EDSS review of the presenting symptoms.

Or

2. New Brain MRI lesion. This will be defined as any new or clearly enlarging T2 lesion felt to be due to MS, regardless of whether it is associated with enhancement after the injection of Gadolinium. Development of new or more overt T1 hypointensities not associated with a new or enlarging T2 lesion will not be considered a new lesion.

A participant will be determined to have achieved the primary endpoint if they have either a new Protocol defined relapse or a new/enlarging brain MRI lesion. If any study participant achieves an endpoint, they will be referred back to

their primary neurologist for consideration of restarting a MS DMT of their choice, or switching to an alternative DMT (if they were in the continuation arm). They will continue to be followed at all study time points with all procedures. This is a pragmatic trial, so individuals will continue to receive care from their primary neurologist (in many cases, this will be the Treating physician/PI as well). At all times, it will remain the choice of the patient and their physician to maintain or change the MS DMT. Any worsened neurological symptoms attributed to MS that are treated with systemic steroids, regardless of characterization above, will be counted as a Protocol defined relapse. In this context, it is imperative that patients contact the local PI of the study first and foremost, so that decisions about the use of steroids may be made by study personnel, and steroids used or not used after the determination of relapse status per the protocol.

An adverse event (AE) is the appearance or worsening of any undesirable sign, symptom, or condition occurring after starting the study even if the event is not considered to be related to study conditions or assignment. Study conditions or assignment includes assignment to continue or discontinue prior DMT. Medical conditions and diseases present before starting the study are only considered AEs if they worsen after starting the study. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of AEs should be sought by nondirective questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All AEs must be recorded in the AEs eCRF with the following information:

1. the severity grade (mild, moderate, or severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final examination)
4. whether it constitutes a serious AE (SAE)

Serious adverse events such as hospital admissions for > 24 hours, new significant medical diagnoses such as cancer (other than basal cell carcinoma), and MS relapse requiring corticosteroid use will be ascertained at each visit. SAEs should be reported to sponsor and entered into the electronic database within 24 hours of the event being reported to the study team. We will collect ongoing side effects of all DMTs, and non-serious adverse events in both groups, and report descriptive statistics and proportions on all adverse events. We will provide confidence intervals for the proportions and test them between treatments groups using the same type of methods used for the primary outcome.

E. Potential Scientific Problems:

Blinding of outcome measures is very important. As this is a pragmatic study, in which the research component is added on to the basic clinical visit, the Treating Physician/PI will have obtained a relapse history as part of that routine visit, yet is not blinded to the patient's medication assignment. The definition of relapse includes performance of the EDSS, and the separate EDSS Examining Clinician will be blinded to medication assignment, as well as to the relapse history, when doing the EDSS. While it might be preferential to have a relapse assessor separate from both the PI and the EDSS rater, this is impractical due to costs, the requirement to have a third clinician available at the visit, and the extra time of the visit. Thus, we will ask the PI to do a relapse assessment based on symptoms, but only make this information available to the EDSS Examining Clinician AFTER the EDSS is completed. The EDSS Examining Clinician will make the final assessment as to whether a Protocol defined relapse has occurred. While MRI readers and Examining Clinicians will be blinded to the patient's medication assignment, patients will not be blinded to medication assignment. Thus interpretation of the secondary Aims and Hypotheses as they relate to PROs will be potentially confounded by patient bias.

Significant efforts will be made to enroll only those patients who are truly willing to be randomized. If an excessive number of patients enter the study attempting to get into one or the other group assignment, they may be more likely to drop out if they do not receive the desired assignment, thus confounding data analysis.

It is possible a patient may have asymptomatic changes on a surveillance spine MRI scan, which is not part of the protocol or SOC. Most new spine lesions will have clinical symptoms and signs associated with them, however, limiting the significance of this issue.

F. Data Analysis Plan:

a. Aim #1: Proposed Data Analysis: We will perform a non-inferiority test for the proportions of the discontinue and continue groups experiencing a binary, protocol-defined disease event within a year. A countable event will be a new protocol-defined relapse, and/or a new brain MRI lesion. We will test the null hypothesis of inferiority with the proportion of disease events for the discontinue group being 0.08 greater (i.e., 0.10 vs 0.02) than the proportion for the continue group under the alternative that the two rates are equal. Because of the expected small numbers of events, we expect to use likelihood based exact binomial methods to obtain a confidence interval for

comparing the proportions. If the upper bound of the 95% confidence interval for the difference between the groups is less than 0.08, then we can rule out discontinuation increasing the disease event proportion by 0.08 or greater. The anticipated small number of events, and the need to use exact methods, will constrain the models that can be used in analyses. Adjustment for center heterogeneity may be attempted with Cochran-Mantel-Haenszel test, but may be similarly limited by anticipated small number of events. We will also calculate estimates and confidence intervals, using exact methods as necessary, for the proportion of disease events in both the discontinue and continue groups. In the unlikely event the proportions are relatively large, we will also calculate estimates and confidence intervals for relative risks. Larger numbers of events would permit the fitting of more complex models

b. Aim #2: Proposed Data Analysis: We will calculate estimates and confidence intervals, using exact methods as necessary, for the proportion of disease events in both the discontinue and continue groups. Aim #2 assesses progression of disability as noted on the EDSS, and this will be defined as an increase of at least one point, confirmed at 6 months, for those with a baseline EDSS ≤ 5.5, or a change of at least 0.5 for those with EDSS of 6.0 or greater at baseline. Outcomes assessed will include % of patients with confirmed progression in each group and mean change in EDSS in each group.
c. Aim #3: Proposed Data Analysis: Descriptive statistics on patient demographics, PDDS, MSIS, performance and NeuroQOL short form scales, and all other PROs will be prepared for treatment group by occurrence of disease event, and qualitatively compared. Pre-Post change will be compared between treatment groups. Change scores will be used for continuous and metric outcomes, and the treatment groups will be compared with two sample T-tests, or Wilicoxon tests if necessary. Binary outcomes, such as dichotomized changes in EDSS and other scales, will be tested with chi-square and proportion tests, or exact analogs if necessary. MSIS will be divided into patients with greater or less than a change of 7.5 (considered a significant change). Correlations between continuous scales will be examined, and compared between treatment groups. Events will also be compared to non-events, and combinations of (event outcome) will be tested for differences, using similar methods, in the unlikely situation there are enough events to permit meaningful statistical analysis (>= 10 samples for an analysis group). Multiple groups can be tested with ANOVA methods for continuous outcomes, and with chi-square tests and logistic regression for binary outcomes.

Sample Size Estimation: Our null hypothesis for AIM #1, inferiority of the discontinue group, is a disease event proportion of 0.02 for the continue group, and 0.10 for the discontinue group. Our alternate hypothesis for the power calculation, non-inferiority of the discontinue group, is a disease event rate of 0.02 for both the continue and discontinue groups. Our study population consists of stable patients, so we expect the disease event rate to be very small for the continue group, and possibly the discontinue group as well. For a target alpha level of 0.025, a sample size of 112 per treatment group (225 total), would achieve 95% power for the non-inferiority test. For a single treatment group with 112 samples, if the true proportion is 0.02, then the upper bound of an exact confidence intervals can be expected to be less than 0.11 more than 95% of the time. Anticipating a dropout rate of approximately 9-15%, we plan to attempt to recruit 132 patients per treatment group (265 total).

It may be that there are differences between those with relapsing forms vs progressive forms of MS after discontinuation of their DMT. While we will not be powered to assess differences separately by relapsing or progressive forms, we have a pre-planned analysis for this important question, as well as other sub-group analyses. These will include analysis based on sex, age, disease duration, time since last relapse, specific DMT, and others. If we stratify by MS subtype, relapsing vs. progressive, and the sample is approximately evenly divided between each treatment group and MS subtype combination, 56 per combination (after drop-outs), then the test for non-inferiority within an MS subtype has 59% power to detect a difference. A non-inferiority threshold of 0.13 for the disease proportion in the discontinue group would achieve 84% power. For a single treatment group, within an MS subtype, with 56 samples, if the true proportion is 0.02, then the upper bound of an exact confidence intervals can be expected to be less than 0.15 more than 95% of the time. Since study outcomes will not be powered for stratification by MS type or heterogeneity of treatment effects, they will be treated as exploratory.

Similarly, we are making the assumption that risk of discontinuation to achieve the primary endpoints in Aim #1 will be similar for different DMTs, and for different subtypes of MS, ie relapsing vs progressive forms. To assess each medication individually would not be possible given the study constraints, and there is no a priori data to consider the risks different in this patient group, ie older, stable patients. While it may not be true, ultimately, that risks of new inflammatory disease activity after discontinuation of DMT are the same in relapsing and progressive MS patients, or that risk of relapse is the same in each group, there is no data on this point in this population, ie older, stable patients. For the purposes of the analysis we are assuming there are no expected differences.

For secondary outcomes AIMS 2-3, a two sample t-test comparing change scores between treatment groups with an alpha level of 0.05 and an effect size equal to 38% of the standard deviation would achieve 80% power, and an effect size of 44% of the standard deviation would achieve 90% power. A two sample proportion difference test between treatment groups with an alpha level of 0.05 and an effect of approximately 0.19 would be able to achieve 80% power, and an effect of 0.22 would achieve 90% power. A relative risk test with an alpha level of 0.05, a control proportion of 0.3

or 0.5, and a ratio of 1.61 or 1.37 respectively would achieve 80% power, and a ratio of 1.71 or 1.42 respectively would achieve 90% power. A Pearson correlation of 0.27, within a group of 112 samples, between two normally distributed variables, would be detectable with 80% power for an alpha level of 0.05, and a Pearson correlation of 0.30 would be detectable with 90% power.

Table 2: Safety Comparisons of the two groups at 25 patients in each group

Sample per Group = 25		
Group	# of Events	Percent
Continue	0	0.00
Discontinue	7	28.00
Proportion Difference Estimate	95% Confidence Interval	
0.2800	0.1067	0.4939

Group	# of Events	Percent
Continue	1	4.00
Discontinue	10	40.00
Proportion Difference Estimate	95% Confidence Interval	
0.3600	0.1311	0.5765

Table 3: Safety Comparisons of the two groups at 65 patients in each group

Sample per Group = 65		
Group	# of Events	Percent
Continue	1	1.54
Discontinue	15	23.08
Proportion Difference Estimate	95% Confidence Interval	
0.2154	0.1083	0.3407

Table 4: pValues in Dark Grey denote statistically significant events in discontinuers (vertical axis) vs continuers (horizontal) at interim analysis of 25 patients in each group.

Sample per Group = 25							
	Null Hypothesis for p (Expected # of Events)						
# of Events	0.02 (0.5)	0.04 (1)	0.08 (2)	0.10 (2.5)	0.12 (3)	0.16 (4)	0.20 (5)
1	0.3965	0.6396	0.8756	0.9282	0.9591	0.9872	0.9962
2	0.0886	0.2642	0.6053	0.7288	0.8195	0.9263	0.9726
3	0.0132	0.0765	0.3232	0.4629	0.5912	0.7870	0.9018
4	0.0014	0.0165	0.1351	0.2364	0.3525	0.5837	0.7660
5	0.0001	0.0028	0.0451	0.0980	0.1734	0.3707	0.5793
6	0.0000	0.0004	0.0123	0.0334	0.0709	0.2002	0.3833
7	0.0000	0.0000	0.0028	0.0095	0.0243	0.0920	0.2200
8	0.0000	0.0000	0.0005	0.0023	0.0070	0.0361	0.1091
9	0.0000	0.0000	0.0001	0.0005	0.0017	0.0243	0.0468
10	0.0000	0.0000	0.0000	0.0001	0.0004	0.0035	0.0173

Table 5: pValues in Dark Grey denote statistically significant events in discontinuers (vertical axis) vs continuers (horizontal) at interim analysis of 65 patients in each group.

Sample per Group = 65							
	Null Hypothesis for p (Expected # of Events)						
# of Events	0.02 (1.3)	0.04 (2.6)	0.08 (5.2)	0.10 (6.5)	0.12 (7.8)	0.16 (10.4)	0.20 (13)
1	0.7310	0.9296	0.9956	0.9989	0.9998	1.0000	1.0000
2	0.3742	0.7389	0.9705	0.9913	0.9976	0.9998	1.0000
3	0.1412	0.4846	0.9009	0.9640	0.9880	0.9989	0.9999
4	0.0414	0.2622	0.7737	0.9004	0.9608	0.9953	0.9996
5	0.0098	0.1185	0.6023	0.7909	0.9031	0.9847	0.9983
6	0.0019	0.0455	0.4205	0.6425	0.8072	0.9599	0.9942
7	0.0003	0.0150	0.2624	0.4776	0.6764	0.9126	0.9841
8	0.0000	0.0043	0.1465	0.3231	0.5261	0.8368	0.9627
9	0.0000	0.0011	0.0734	0.1987	0.3775	0.7321	0.9241
10	0.0000	0.0002	0.0332	0.1112	0.2492	0.6058	0.8628
11	0.0000	0.0001	0.0136	0.0567	0.1512	0.4711	0.7771
12	0.0000	0.0000	0.0051	0.0264	0.0844	0.3428	0.6699
13	0.0000	0.0000	0.0017	0.0113	0.0434	0.2328	0.5494
14	0.0000	0.0000	0.0005	0.0044	0.0206	0.1474	0.4265
15	0.0000	0.0000	0.0002	0.0016	0.0090	0.0870	0.3124
16	0.0000	0.0000	0.0000	0.0005	0.0037	0.0478	0.2154
17	0.0000	0.0000	0.0000	0.0002	0.0014	0.0246	0.1396
18	0.0000	0.0000	0.0000	0.0000	0.0005	0.0118	0.0850
19	0.0000	0.0000	0.0000	0.0000	0.0002	0.0053	0.0486
20	0.0000	0.0000	0.0000	0.0000	0.0000	0.0022	0.0261
21	0.0000	0.0000	0.0000	0.0000	0.0000	0.0009	0.0132
22	0.0000	0.0000	0.0000	0.0000	0.0000	0.0003	0.0063
23	0.0000	0.0000	0.0000	0.0000	0.0000	0.0001	0.0028
24	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0012
25	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0005

G. Summarize Knowledge to be Gained:

There are several ways in which this study might improve health care and outcomes. First, the results will help inform decision-making regarding the duration that MS DMTs remain beneficial, or that benefits no longer exceed the risks

or costs. Patients and their physicians will have controlled, prospective data regarding risk of relapse, new MRI lesions, and progression of disability in patients who both continue and discontinue MS DMTs. They will be able to compare these outcomes and risks with PROs which ascertain quality of life and other measures of patient symptoms, and place them in the context of potential fears about discontinuation, allowing them to determine if ongoing use of MS DMTs remains beneficial and makes sense for them. Second, data from this and related studies may aid insurers in further defining rational policies that focus resources where they are best utilized. Third, this study will help researchers design future studies to define more specific attributes of MS patients and DMTs that are relevant to DMT use and potential discontinuation. Fourth, this study will aid researchers and pharmaceutical companies in development of outcome measures that are relevant to patients. Fifth, this research may guide legislators and regulators in designing laws and rules that protect access to MS DMTs, especially if discontinuation is associated with substantial risk. Finally, the data from this study will assist funding agencies such as PCORI, NIH, NMSS and others in defining funding priorities.

To date, discontinuation of MS DMTs has been studied very little, resulting in patients and physicians struggling to define a logical plan for a discontinuation trial of their own. Thus, no matter the outcomes, it is highly likely that we will produce data that will have an immediate impact for patients and other stakeholders. The most important question we address is to define the risk aspect of the equation when patients and caregivers try to balance the risks and benefits of ongoing use of the DMTs. It is probable that we and other interested parties will want to expand on the findings, especially looking at greater length of study or a variety of additional sub-populations of MS, (e.g., those with varied disease durations, different age groups, different durations of stability, populations stratified by one or more specific DMTs or disease severity as measured by clinical or MRI patterns, restricted MS subtypes, in different countries, or even different diseases with similar needs).

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