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Protocol #: **20-2772**
Project Title: **Discontinuation of Disease Modifying Therapies (DMTs) in Multiple Sclerosis (MS): Extension of the DISCOMS Study**
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I. Hypotheses and Specific Aims:

Main hypothesis: The DISCOntinuation of disease modifying therapies (DMTs) in Multiple Sclerosis (MS-DISCOMS) study is a maximum two-year, randomized controlled clinical trial (RCT) assessing whether relatively older (55+), stable (no relapse for 5+ years, no new magnetic resonance imaging abnormalities of the brain or spine for 3+ years) MS patients who discontinue their DMT have no greater recurrence of disease activity compared to those who continue use of their DMT. We propose an extension of this trial in a 100-person subset of those from the original study who remain in their original drug assignment group at the end of the primary DISCOMS trial in order to continue to assess the duration of follow-up to more fully answer the question of the duration of safe withdrawal if that is the case. To date, the DSMB has not stopped the study, and the final participants have not completed the trial as yet. Thus, we have no new information on the equipoise of the original hypothesis. The **Main Hypothesis of this extension trial** is that among those who have successfully discontinued their DMT as part of the DISCOMS trial (i.e. did not have a new MS relapse or brain MRI lesion) and remain off DMT after DISCOMS are at no greater risk of new or worsened MS disease activity compared to those who successfully continued their DMT as part of DISCOMS and remain on DMT, each assessed at least one year after termination of the primary DISCOMS study.

Specific Aims:

In MS patients who participated in the primary DISCOMS trial, successfully completed a minimum of 18 months of the two year primary DISCOMS study and remained in their original assignment group (i.e. either have discontinued or continued their DMT or another DMT), we will compare clinically significant and patient-relevant outcomes in those who have persistently discontinued vs persistently continued DMTs to determine if:

1. Risk of new relapses or brain MRI lesions is no worse in those persistently discontinuing
2. Risk of disability progression (by the Extended Disability Status Scale - EDSS) is no worse in those persistently discontinuing
3. Cognition, quality of life and other patient-reported outcomes (PROs) are no worse in those persistently discontinuing

II. Background, Preliminary Studies, and Significance:

Multiple sclerosis (MS) is a debilitating neurologic disorder that is now estimated to afflict over 700,000 and perhaps over 900,000 people in the US.[1] At onset, it most often affects young people in the prime of their lives, with a median age of onset around 30,[2] but 46% of adults in the US with MS are 55 or older.[1] 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]

MS symptoms and disability result from a combination of CNS inflammation and neurodegeneration over time.[6] Acute bouts of inflammation are 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, 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 classes of molecules and 25 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 through 2018).

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] Indeed, since the approval of Siponimod, the FDA has been approving all DMTs studied in relapsing forms of MS for use in clinically isolated syndrome (CIS), relapsing-remitting MS, and secondary progressive MS ***with activity***. Thus, the presently-available 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 generally 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 or risks 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 trials in SPMS or PPMS (often negative in outcome) 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 recently surveyed 1000 individuals within the North American Research Committee on Multiple Sclerosis (NARCOMS), and of 377 who responded (average age 56, and average time on most recent DMT greater than five years), only 11.9% responded that, if their disease was felt to be stable, they were likely or very likely to consider a trial off DMT[55]. Thus, even with disease stability, or perhaps because of stability, many over the age of 55 are reluctant to consider discontinuing their MS DMT. This study will provide evidence on the safety and tolerability of a discontinuation decision that can help patients decide if there is time in which the risks of therapy may be balanced against benefits.

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.[56] 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, [57] 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[58]. 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 outweigh the risks and costs of use remains unclear. Development of antibodies against the DMT,[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, and just one[65] of these studies was a randomized, controlled discontinuation trial. 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 and might not benefit from an anti-inflammatory medication. For comparison, in a 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 who 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.

Over the last decade a number [68-74] of observational studies have addressed the question of what is the risk of disease recurrence when individuals discontinue their DMTs. Age ranges and reasons for discontinuation have been broad, some with mean ages as young as 38 or 45, and most have been uncontrolled (a couple have included propensity matching, comparing stoppers to stayers) [68,74]. The overall conclusions from these studies are several: the greatest risk of relapse recurrence is in younger (especially under age 45) patients with recent relapse and/or Gad-enhancing lesions on MRI; and progression of disability is mostly seen in older patients with higher levels of disability at

the time of the discontinuation. There is conflicting data as to whether there might be a small increase in disability among those who discontinue vs continue their DMT. [68,74] Further, some hypothesize that the disease has two phases, the inflammatory phase and the progressive deterioration stage, the later for which we currently have no treatments. Understanding the durability of treatment versus the disease course as measured by activity and deterioration is important to more fully understand.

Potential discontinuation of DMTs in MS also has been the subject of an Agency for Healthcare Research and Quality (AHRQ) Comparative Effectiveness Review (Number 150)[75] 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, in 2016, a significant information gap existed 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.

To address the above gaps in knowledge, we designed and are close to finishing an original 2-year, randomized, controlled 1:1 RCT (continue vs discontinue), rater-blinded DMT discontinuation study (DISCOMS, NCT#: 03073603). The last of 260 patients was enrolled on February 4, 2020. Last patient, last visit will be in August 2021 (**note, not all will be followed for two years, with shortest final follow-up at 18 months in a minority of late enrollees**). While this is the first RCT of DMT discontinuation, others are underway in France (NCT03653273) and The Netherlands (NCT04260711). Among focus groups employed during the operation of DISCOMS, it was very clear that one of the main limitations of the study was relatively short duration of the follow-up. Herein we propose to address this limitation with a non-randomized, yet rater-blinded protocol to extend the follow-up of 100 participants from the original DISCOMS cohort by at least 12 months. In essence, the first 100 participants from the DISCOMS primary study who have already successfully completed the primary DISCOMS study (i.e. did not fail on the primary outcome of a new relapse or Brain MRI lesion), retained their original drug assignment (continue or discontinue) at the end of their participation in DISCOMS, and agree to participate in the extension will be included for a minimum of 12 more months of follow-up as assessed at a single visit. This is a pragmatic clinical trial, based on real world patterns of patient decision-making. As such, study visits will be attached to routine office visits when possible, and the patient/their insurance will be responsible for payment of standard of care aspects related to the study. This will include drug costs, the annual brain MRI scans at year one, and all routine safety monitoring as would be obtained in a typical office setting for that individual medication. The funding agency, EMD Serono (a biopharmaceutical business of Merck Pharmaceuticals KGaA), will be responsible financially for all research aspects, including data acquisition, all research personnel, and all regulatory review. In addition, while this is a discontinuation trial, all patients will be aware of their medication assignment, while 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 new 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 greatest impact upon. 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.[76] 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. This will also allow us to compare the change in disability over

the duration of the trial in those who were able to maintain their treatment assignment without inflammatory activity.

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.[77] 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. 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. 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[78] 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.[80] 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.[81]
   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 questions were 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 questions 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 extension 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 extension 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:

- Participation in and completion of the DISCOMS trial (NCT# 03073603) for a minimum of 18 and maximum of 24 months (i.e., it is possible some will have been enrolled late enough in the primary study so as to not have completed the full 24 months).
    - Only include participants in the following study groups:
        - Randomized to the discontinue group, stayed off their DMT throughout and after the trial
        - Randomized to the continue group, continuously* stayed on their DMT throughout and after the trial
- Must be willing to continue in their previously-assigned treatment group for the entire, additional 12-Month follow-up period. For those in the continue group, the participant may have switched to a generic or biosimilar version of their medication, or to a different approved medication, if due to intolerance, convenience or insurance mandates, but NOT if due to having new or worsening MS disease activity.
- 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.
- During the primary DISCOMS study, no evidence of recent new inflammatory disease activity (inactive by the Lublin criteria[16]). Pseudorelapses due to infection, fever, or other stressors as deemed by the local PI will NOT be excluded. Those who have already successfully completed the primary DISCOMS study without having a new relapse or MRI scan change, but who have a relapse or scan change AFTER ending participation in DISCOMS but before entering the extension ARE eligible and will be recruited, i.e. we do not wish to undercount new activity that occurs after exiting DISCOMS.
- Provides informed consent to continue in the extension trial.
- Willing to follow the protocol.
- Able to undergo a brain MRI without anesthesia, as part of routine care (i.e. paid for by their insurance).

* 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:

- During original DISCOMS trial participant was randomized to the discontinue group, but then either re-started their DMT during the trial (study-defined 'treatment withdrawal), or wishes to restart their DMT after completing original DISCOMS study. Conversely, also excluded are those who completed the primary trial in the continue group and then discontinued, or wishes to discontinue, after completion of the primary study.
- Any MS relapse or new MRI scan lesion (3 mm or larger) during the primary DISCOMS trial, with relapse determined by the blinded examiner and MRI lesion determined by the blinded MRI reader.
- Significant (as defined by the PI) intolerance of presently-used DMT, if taking a DMT
- The following must **not** have occurred during the original DISCO MS study or since completing the study:
    - Use of any non-FDA-approved DMT
    - More than two courses of acute, systemic (IV or oral). 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. Any use of steroids to treat MS relapse, possible relapse, or pseudo-relapse is excluded. Inhaled or topical steroids for non-MS are not exclusionary.
    - Use of alemtuzumab, mitoxantrone, cyclophosphamide, methotrexate, cyclosporine, rituximab, or cladribine.
    - Use of any experimental agent used as a DMT for MS
    - Cancers other than basal cell skin cancers
- Other significant medical or psychiatric illness, if uncontrolled. Examples: uncontrolled hypertension, uncontrolled diabetes, uncontrolled asthma, uncontrolled depression.
- Unable to give informed consent or follow the protocol.
- Unable to undergo brain MRI.
- 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 non-randomized, rater-blinded pragmatic trial, which is an extension of the randomized discontinuation trial (RDT)[82], DISCOMS. While RDTs have been done in cancer[83,84] and rheumatoid arthritis patients,[66] the original DISCOMS protocol was the first such study in MS. For this protocol, a subset of 100 subjects of the original 260 enrolled will be followed. Study sites will be limited to the top 10 recruiting sites across the United States from the DISCOMS study due to financial and cost-effectiveness issues. Those sites will have participants who have completed 18-24 months of the primary study. In practice, the vast majority, if not all, will have completed 24 months. We will explicitly include any who have completed, including those who already have exceeded 12 additional months after completion of the primary trial. Individuals who have successfully completed (retained original drug assignment and did not meet the primary endpoint of DISCOMS) the primary DISCOMS trial and are willing to retain their original drug assignment after completion and for an additional 12 months will be offered entry into the extension. The only exception to that will be individuals who continued the original drug assignment during and after the primary trial, up to 24 months, but who then had a relapse, new MRI lesion, or other MS-related reason between months 24 and 36 which resulted in their change of medication assignment. These individuals can and should be included, and counted as "failing" during the extension trial completing the Kaplan-Meier event free survival curve critical to the original hypothesis. A total of up to 100 patients will be consented and enter the extension trial, regardless of assignment, on a first come first serve basis to avoid selection biases to the extent possible. The intent is to take the first 100 who fulfill criteria and agree to participate. The plan is for a 50/50 distribution, but there may not be exactly 50 in each group. As of December 15, 2020, 123 had completed participation of the primary 24-month study, and information as to DMT use plans after finishing 2-years participation in DISCOMS was available for 84/123, 42 in each group (see Table 1 below). Notably, in the Discontinue group, 86% remained off DMT while only 60% in the Continue group plan to remain on a DMT (23/42 on the same DMT, two switching to an alternative). Overall 73% remained in the primary assignment grouping. If these ratios stay consistent as more finish DISCOMS, discontinuers will account for roughly 59% of the total enrolled in the extension trial. Also, of the 123 completers, 49 have also gone at least an additional 12 months since completion of DISCOMS, and they will be offered entry into the extension trial, should they otherwise fulfill criteria. There will be no placebo and no sham treatment. (Please see the statistics section the extension ns for power analyses discussions).

Table 1. Use of Disease Modifying Therapy after two years of participation in DISCOMS.

Continue	Stop my DMT	17
	Continue my current DMT	23
	Switch to a new DMT	2
Discontinue	Stay off my DMT	36
	Restart a prior DMT	5
	Restart a new DMT	1
	Total	**84**

The study procedures will be slightly different for those who are completing Month 24 of the primary trial and simply "rolling over" to extension on the same day, compared to those who already have completed the study. For those rolling over at Month 24, they will be offered participation in the extension trial. If they agree to participate, they will do a second study visit at the Month 24 visit, which concurrently will be Time Zero (T_0) for the extension. This will consist of obtaining informed consent and going through Inclusion/Exclusion criteria. All the data from Month 24 visit will comprise the baseline data for the extension. Current and past DISCOMS study participants will be identified and screened for eligibility. This may include individuals who already have surpassed a full year since last participation in the trial, so long as they continued their original group assignment after the completion of the primary study and for at least for one additional year, or until they had a relapse or new MRI lesion, as determined in screening. These individuals will explicitly be included, upon verification of the defining event. Patients will be approached at their next study visit or by phone (if they've already completed the original study) by the PI and/or a study coordinator about participating in the study. The local PI for the study will verify accuracy of meeting inclusion criteria, and screening and consent may take place in person or by electronic means. Participants must agree to have a single SOC, month 36 MRI done by their primary neurologist and have the results and the MRI disk sent to the study site, to be assessed by a blinded central reader as has been done during the primary trial. All research visits will be conducted at the same time as SOC visits when possible, or as separate visits if not possible or the patient receives SOC elsewhere. For those who have exceeded 30 months from onset in the primary trial, the P_1 visit (a telephone call) will not occur. All patients will undergo the T_1 visit at 36 months, or longer should they have already exceeded 36 months from onset of their participation in the primary trial.

Please see Table 2 below for the schedule of study activities.

Table 2: Schedule of Research Assessments

DISCO MS Extension Assessments	T_0 (Baseline)*	P_1 (30 Months after enrollment in original study, +/- 14 days)**,****	T_1 (36 Months after enrollment in original study, visit window is -1 month/+18 months)****	Unscheduled Visit
Informed Consent	X	-	-	-
Inclusion/Exclusion	X	-	-	-
Vitals	-	-	X	X
Prior/Con Meds	-	X	X	X
Adverse Events	-	X	X	X
Comorbidities	-	-	X	X
Neuro-QoL Short Form	-	-	X	X
PDDS	-	-	X	X
SymptoMScreen	-	-	X	X
MSIS-29	-	-	X	X
SDMT	-	-	X	X
Treatment Satisfaction Question	-	-	X	X
Treatment Decision Questions	-	-	X	X***
Relapse Assessment (blinded rater)	-	-	X	X
EDSS (blinded rater)	-	-	X	X
MRI (Standard of Care)	-	-	X	-

*T_0, Baseline visit, can occur on same day as T_1.
** If the participant enters the extension study 30 months+ from onset in the primary trial, P_1 will not be performed.
***If the Unscheduled visit will be the final visit, i.e. if the participant is discontinuing the study after their unscheduled visit, administer the Treatment Decision Questions (TDQ). If the participant will continue participation and will have a T_1 visit, do not administer the TDQ at the unscheduled visit.
****Some participants' final study visit for the original DISCO MS study will be at 18 Months. For these subjects, the P_1 visit will occur 24 Months after enrollment in the original study, and T_1 will occur 30 Months after enrollment in the original study.

A thorough discussion of the trial, signing the informed consent form, and confirmation of inclusion/exclusion criteria will be completed during the baseline visit (T_0). Consenting may be done in-person on paper or using e-consent. If utilizing e-consent, participants will be presented a consent form ahead of time, and upon signature in the REDCap system, participants will receive a pdf of what they 'signed' electronically via REDCap. A pdf will also be generated for study records. T_0 may occur on the same day as T_1 if the patient has already completed the main DISCOMS study and is within the window for the Month 36 visit. There will be one phone call (P_1), conducted by the study coordinator, at 30 Months post-enrollment in the original DISCO MS trial. On this phone call, the participant will be asked about any new or ongoing adverse events, changes to medications, and any symptoms suggesting a potential relapse. If the participant joins the Extension study after they already passed 30 Months post-enrollment in the original DISCO MS trial, they will not do P_1. Those who have already exceeded 30 months since starting the primary DISCOMS trial will have the equivalent of the phone assessment at the T_0 visit. Participants will come in for 1 additional study visit: T_1 at 36 Months post-enrollment in the original DISCO MS trial. During T_1, patients will undergo a blinded EDSS exam and relapse assessment, vitals, complete an SDMT assessment, and will complete all PROs/comorbidities. All PROs/comorbidities may be completed on paper in person or remotely via the electronic platform within the visit window, based on site and patient needs. Participants will also undergo a standard of care MRI scan of the brain at T_1, within 60 days before and 120 days after the study visit. Participants who have already exceeded 12 months from the end of the primary trial will still be recruited and simply do the T_1 visit at their earliest convenience. The maximum window will be 30 months after completion of the primary study, or 54 months since starting DISCOMS. Participants should always be brought in as close to 36 months as possible. Some participants' final study visit for the original DISCO MS study will be at 18 Months. For these subjects, the P_1 visit will occur 24 Months after enrollment in the original study, and T_1 will occur 30 Months after enrollment in the original study.

All participants will undergo the T_1 visit, which will include a formal, blinded relapse assessment by the Examining Physician (EDSS rater) in conjunction with the PI (see section E). Prior to enrollment, the enrolling physician will certify, based on their personal review of the prior MRI scans and/or reports which will include data from the 24 month primary DISCOMS trial, that the scans have been stable for a minimum of 4.5 years (review of minimum of two scans, although it could be more, separated by at least 4.5 years). MRI scans at T_1, 36+ months after onset of participation in the primary trial, 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 on a MRI machine with magnet 1.5 Tesla or greater, with and without contrast. Gadolinium may be withheld at the discretion of the PI or request of the patient. The window for T_1 MRIs will be 60 day before or 120 days after the T_1 study visit, and will be analyzed by a central, board-certified, blinded neuro-radiologist for new activity compared to prior scans. 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 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:

In the primary DISCOMS trial, we employed a five person Data Safety Monitoring Board composed of a patient, a statistician and three neurologists to assess safety within the study every 6 months and generate a formal report concluding it was appropriate, or not, to continue the study. As of 9/14/2020, they have concluded in each report there were no reasons to discontinue the study. As there have been no significant safety issues, and many of the potential enrollees in the extension trial will have already finished their participation, we will simplify things in the extension trial here. A Medical Monitor will be employed to perform twice yearly reviews of the safety 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 (i.e., higher than prior baseline) of disease activity.[63-65]

It is possible that data from the primary DISCOMS trial will become available before the end of participation by those in the extension trial. Whatever the outcome: if the data will conclude that those who have discontinued DMT have an inferior outcome compared to those who continued DMT or if the trial concludes there is no evidence of a difference to date, all participants still in the extension trial will be given results of the primary DISCOMS study by telephone, or email if they do not answer the phone, within two weeks of generation of the primary outcome data. They will be asked to verbally (or by email) consent to continue participation at that time. At least three attempts will be made to contact participants by a combination of the two techniques, phone or email. These attempts and the participants' responses will be documented in the source documents and electronic data capture system. As there is only a single visit at 12 months after signing the consent for the extension trial, no reconsent beyond this will be performed. This verbal/email reconsent possibility will be included in the original consent of the extension trial. Regardless of their treatment decision after learning the results of the primary DISCOMS trial, they will be followed to the end of the extension trial with the treatment as they choose in response to the primary results.

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, i.e. 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 once at the 30 month time period 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 at least 3 mm in size 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 the 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.

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.

This protocol, if taken as an independent study of participants who have been randomized and followed on treatment or off treatment for two years for an additional follow-up period will not have sufficient power to answer the question of non-inferiority during this extension period. If taken as a continuation of the original protocol, it then operates under the power considerations designed in the original protocol (NCT03073603). We acknowledge the insufficient power of this extension study to address non-inferiority, but still expect to obtain valuable information. Through this extension, we will be able to track rates of relapse or MRI scan changes and collect information on effects of withdrawal from therapy, disease progression, and quality of life of these older MS participants over a longer follow-up period.

F.Data Analysis Plan: 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 100 finishing participants, this will allow an attempt at subgroup analysis by sex, age epochs, disease duration, and others. Patients with all forms of MS, RRMS, SPMS and PPMS who participated in the original DISCOMS trial 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 sub-analysis.

a. Aim #1: Proposed Data Analysis: We will perform an extension of the primary DISCOMS study, that being the time to failure defined as a protocol-defined disease event with each treatment group extending the understanding of the durability of the assigned treatment arm beyond the original DISCOMS follow-up period. A countable event will be a new protocol-defined relapse, and/or a new brain MRI lesion. We will estimate the long-term differences between the two treatment arms. Further by linking the time to event within the 100 participants with the original DISCOMS event free survival estimates, we can further evaluate the null hypothesis of inferiority with the proportion of disease events for the discontinue group being 0.08 proportion worse (our original noninferiority margin) at later time points of follow-up 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 will use Kaplan-Meier estimates of the differences to obtain a confidence interval for comparing the proportions with individuals counted at their respective event times or censored based on their last known status. If the upper bound of the 95% confidence interval for the difference between the groups is less than 0.08, then we can reject inferiority and rule out discontinuation increasing the disease event proportion by 0.08 or greater. Our primary goal here is to estimate these differences given the relatively small sample size included, but we will calculate these values using the data obtained. 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, but to date we know that the majority have not failed although their assignments are not known to us.

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 after this extension

study. Aim #2 will be mostly descriptive and 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. The estimates of the population from the origin of the study will be model based since participants in the extension study must by criteria have not had progression over the initial period of follow-up. Nevertheless, we will have the proportion at the end of the formal DISCOMS study and can apply the successive failure rates using conditional probability to obtain an overall estimate of the progression rate after 2 or 3 years and further can compare the post DISCOMS experience between the two arms given the participants were free of events at entry into the Extension study. Outcomes assessed will include % of patients with progression in each group as compared to the final EDSS in DISCOMS, and mean change in EDSS in each group overall (via the extension period. The latter analyses will help identify if the rate is increasing over time or if the rate is relatively stable over time.

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 changes, from baseline and from the entry into the Extension study (with the randomization maintained) 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 methods as 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: The sample size was driven by budget considerations and the expected number who could complete the extension within a reasonable time period. We chose to focus on those who have been maintained in their assigned treatment arms from the original randomization to allow extension of time to event analyses. We considered including those who would go back on therapy or who subsequently stopped therapy, but felt that not only would the numbers likely be smaller than desired, they would diminish the available slots for the most informative participants (those maintaining their randomized assignment). Thus, while we expect roughly equal numbers from both treatment arms (the alternative hypothesis originally posed, that the two treatments are equal), we will have approximately 50 participants per arm. If we assume that there are 50 participants in each arm and 20% of the discontinue arm fails compared to 6% (10 and 3 of each group respectively), a fisher's exact test would yield a one sided p-value of 0.036, sufficient to say the discontinue group has done worse. We also plan to test for baseline differences between the two groups, using data from the original RCT, and will adjust for any significant baseline differences.

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 descriptive analyses 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 since study outcomes will not be powered for stratification by MS type or heterogeneity of treatment effects, they will be simply examined as estimates of longer term treatment follow-up.

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, i.e. 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, i.e. 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 are no data on this point in this population, i.e. 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 estimates of the differences in change scores between treatment groups will be calculated for describing the longer term follow-up.

We will continue to assess safety as was done during the primary DISCOMS trial to ensure there are no late effects or concerns developing. We will continue to monitor AEs and SAEs including those which occur from the discontinue group if they return to treatment.

G.Summarize Knowledge to be Gained:

There are several ways in which this study might improve health care and outcomes. First, by extending the follow-up period of the original DISCOMS trial, we will be providing additional information about the potential long-term risks or benefits of discontinuing DMTs for older MS patients. 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). Indeed, two other RDTs in MS are now underway, in France (SPMS aged 50 and older, NCT03653273) and the Netherlands (age 18+ RRMS, NCT04260711).

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