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Citation for final published version:

Ontaneda, Daniel, Tallantyre, Emma C. , Raza, Praneeta C., Planchon, Sarah M., Nakamura, Kunio, Miller, Deborah, Hersh, Carrie, Craner, Mathew, Bale, Clare, Chaudhry, Burhan, Gunzler, Douglas D., Love, Thomas E., Gerry, Stephen, Coles, Alasdair, Cohen, Jeffrey A. and Evangelou, Nikos 2020. Determining the effectiveness of early intensive versus escalation approaches for the treatment of relapsing-remitting multiple sclerosis: The DELIVER-MS study protocol. Contemporary Clinical Trials 95 10.1016/j.cct.2020.106009

Publishers page: http://dx.doi.org/10.1016/j.cct.2020.106009

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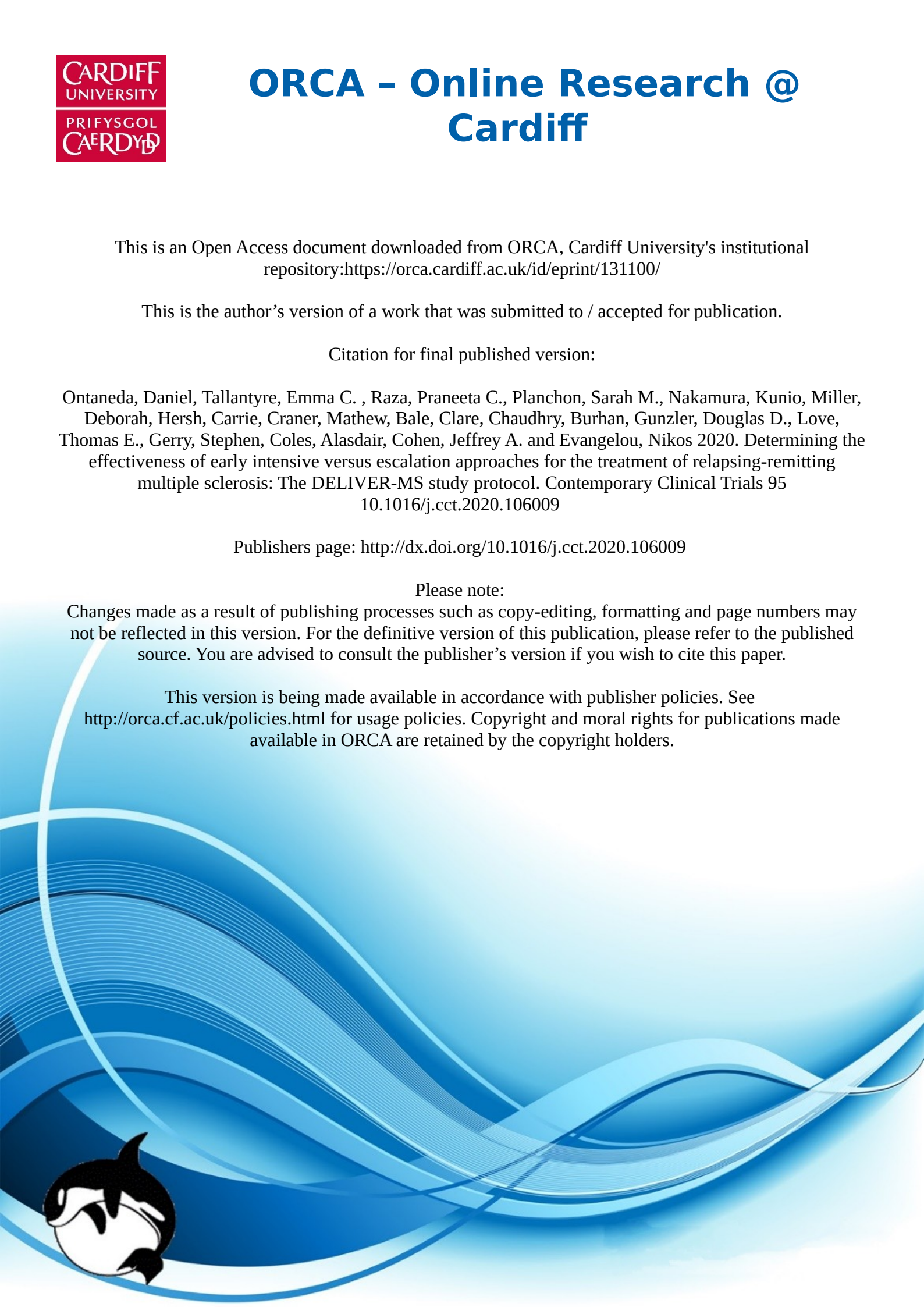

Title: Determining the Effectiveness of early Intensive Versus Escalation approaches for the treatment of Relapsing-Remitting Multiple Sclerosis: The DELIVER-MS Study Protocol

Daniel Ontaneda MD MSc[1], Emma C. Tallantyre BMBS, PhD[2], Praneeta C. Raza MD MSc[1], Sarah M. Planchon PhD[1], Kunio Nakamura PhD[3], Deborah Miller PhD[1], Carrie Hersh DO MSc[4], Mathew Craner MB ChB PhD[5], Clare Bale MS PhD[6], Burhan Chaudhry MD[7], Douglas D Gunzler PhD[8], Thomas E Love PhD[8], Stephen Gerry BSc MSc[9], Alasdair Coles BM BCh PhD[10], Jeffrey A. Cohen MD[1], Nikos Evangelou MD DPhil[11]

1. Department of Neurology, Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, Ohio, United States
2. Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, Wales, United Kingdom.
3. Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, United States
4. Lou Ruvo Brain Center, Cleveland Clinic, Las Vegas, United States
5. Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom
6. University of Nottingham, Nottingham, United Kingdom
7. Department of Neurology, University of Missouri, Columbia, MO, United States
8. Center for Health Care Research & Policy, Case Western Reserve University at MetroHealth Medical Center, Cleveland, Ohio, United States
9. Centre for Statistics in Medicine, University of Oxford, United Kingdom
10. Neuroscience Department, Cambridge University, United Kingdom
11. Clinical Neurology, Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom

Corresponding Author:
Daniel Ontaneda
9500 Euclid Ave, U10 Mellen Center
Cleveland, Ohio, USA, 44195
ontaned@ccf.org
Tel: 216-444-0151
Fax: 216-445-7013

Keywords:
Multiple sclerosis
Relapsing Remitting
Early highly effective treatment
Escalation approach
Clinical trial
Disease modifying therapy

Word Counts:
Abstract: 239 (max 250)
Introduction: 456 (max 500)
Discussion-section: 1080
Total Word Count: 4857

Note: There are no word limits for the other sections of the paper.

Disclosures

DO: has received research support from the National Multiple Sclerosis Society, National Institutes of Health, Patient Centered Outcomes Research Institute, Race to Erase MS Foundation, Genentech, Genzyme, and Novartis. He has also received consulting fees from Biogen Idec, Genentech/Roche, Genzyme, Novartis, and Merck.
ET: has received honoraria from Novartis, Biogen, Roche and Merck, and has received expenses to travel to educational meetings from Merck and Roche.
PCR: Nothing to disclose
SMP: nothing to disclose
KN: has received research support from National Multiple Sclerosis Society, National Institutes of Health, Patient Centered Outcomes Research Institute, Novartis, and Sanofi Genzyme and received licensing fee from Biogen.
DM: shares rights to intellectual property underlying the Multiple Sclerosis Performance Test, currently licensed to Qr8 Health and Biogen.
CH: has received speaking and consulting fees from Biogen Idec, Novartis, Genentech/Roche, Genzyme, and EMD Serono. She has received research support paid directly to her institution from Biogen Idec, Genentech and PCORI.
MC: has received research support from Multiple Sclerosis Society (UK) and unrestricted grants from Biogen, Roche, and Novartis, He has also received honoraria for educational meetings and/or consultancy from Roche, Merck, Biogen, Novartis and Genzyme
CB: Nothing to disclose
BC: reports speaking and consulting fees from Biogen Idec, Genentech/Roche & Genzyme
DDG: reports a book royalty agreement with Taylor Francis Publishing
TEL: Nothing to disclose
SG: Nothing to disclose
AC: honoraria and travel expenses from Genzyme/Sanofi company
JAC: personal compensation for consulting for Convelo, Mylan, and Population Council; and serving as an Editor of *Multiple Sclerosis Journal.*
NE: has received research support from the Multiple Sclerosis Society UK, National Institutes of Health Research UK, Patient Centered Outcomes Research Institute. He has also received consulting fees from Biogen Idec, Roche and Merck.

Abstract

Multiple Sclerosis (MS) is a common cause of neurological disability among young adults and has a high economic burden. Currently there are 18 disease modifying agents for relapsing MS, which were tested in clinical trials versus placebo or an active comparator in a pairwise manner. However, there is currently no consensus on the fundamental principles of treatment approach and initial therapy selection. These factors result in variable use of disease modifying therapies. Here we describe the study protocol for Determining the Effectiveness of earLy Intensive Versus Escalation approaches for the Treatment of Relapsing-remitting Multiple Sclerosis (DELIVER-MS). The main objective of the study is to determine whether an early highly effective treatment approach, defined as use of one of four monoclonal antibodies as initial therapy, is more effective than an escalation treatment approach (any other approved medication as initial therapy with subsequent escalation to higher efficacy treatments guided by radiological and clinical evaluation). The primary endpoint of the study is reduction in normalized brain volume loss from baseline visit to month 36 visit using MRI. Brain volume loss was selected as the best short-term predictor of long-term clinical disability. A total of 400 participants will be randomized 1:1 using minimization to account for age and sex by site, and 400 will be enrolled into a parallel observational cohort. The study results will help guide overall treatment philosophy and will have important implications for patient choice, clinical practice, and treatment access.

1. Introduction

Multiple sclerosis (MS) affects approximately 1 million people in the United States (US) and is a common cause of disability in young adults. [1], [2]. MS has a high economic burden with a lifetime cost of approximately $4 million per patient with a significant portion attributable to medication costs [3], making comparative effectiveness research in MS important. Relapsing remitting MS (RRMS) is the most common form of the disease and is clinically characterized by discrete episodes of neurological impairment (relapses), which have an acute and unpredictable onset [4]. Relapses are the result of development of focal areas of inflammatory demyelination within the central nervous system (CNS). Relapse rate and degree of recovery after relapses predict long-term disability [5]. Significant advances have been made with development of immunomodulatory disease modifying therapies (DMTs), which may prevent the accrual of disability through reduction of new lesion formation and prevention of relapses. In the US, there are over a dozen DMT compounds approved to treat relapsing forms of MS; however, their efficacy to suppress relapses varies (Table 1), and differences in the tolerability and convenience of DMTs, in particular the complex safety profiles of the most effective DMTs, adds challenges to decision-making. There is little information on how different treatment algorithms affect long-term outcomes, and initial DMT choice is highly variable.

<<TABLE 1 APPROXIMATELY HERE>>

The comparative effectiveness and long-term benefits of MS DMTs are currently unknown. Patients newly diagnosed with RRMS and neurologists are currently faced with the dilemma of adopting one of two treatment approaches:

- An “escalation” approach: starting therapy with a DMT that is considered safe but with a modest likelihood to control the patient's MS activity, and escalating to more potent therapies in the face of continued disease activity.

- An early highly effective treatment (EHT) approach, in contrast, involves giving a high-efficacy drug first-line, with greater likelihood of disease control but also rare potential for significant adverse effects.

There is a paucity of studies examining the initial choice of DMTs in RRMS. Comparing individual therapies pairwise is cost-prohibitive and the anticipated approval of new MS medications (not available at the time of trial initiation), decreases the overall impact of such studies. The determination of comparative efficacy across approved treatments is inherently difficult; however, examining overall treatment strategies is feasible in a randomized design and could provide results that are broadly applicable. Therefore, Determining the Effectiveness of earLy Intensive Versus Escalation approaches for the Treatment of Relapsing-remitting Multiple Sclerosis (DELIVER-MS) seeks to study two different general treatment algorithms, an escalation approach versus an EHT approach, both commonly used in MS but that differ considerably in underlying philosophy. By comparing the effectiveness of two general DMT algorithms, we anticipate results that will be widely applicable to current and future DMTs.

2. Methods

2.1 Study Design

DELIVER-MS is a multicenter pragmatic parallel group, open label, rater blinded, randomized clinical trial. 400 participants will be randomized in a 1:1 ratio to an EHT approach as initial therapy after diagnosis (alemtuzumab, natalizumab, rituximab, or ocrelizumab at clinician and participant discretion), or escalation approach (any approved DMT except alemtuzumab, natalizumab, rituximab, or ocrelizumab as initial therapy with subsequent escalation to any approved DMT as indicated). The study is conducted across 24 sites in the United Kingdom (UK) and US. All treatments used are in accordance with local practice and DMT costs are covered within regular clinical practice. Only Food and Drug Administration (FDA)/National Health Services (NHS) approved therapies are used, with the exception of rituximab, for which

an investigational new drug exemption was granted given the frequent off-label use of this medication in clinical practice in the US. Study visits include clinical assessments, cognitive testing, MRI, and patient reported outcome measures (PROMs) at Baseline, 12 months, 24 months, and 36 months.

400 participants total will be recruited for the randomized controlled trial (RCT). Up to 400 additional participants unable to obtain coverage for a medication in their randomized arm or not agreeable to randomization will be recruited for an observational cohort, which includes an identical assessment schedule as the RCT, without randomization. The recruitment flow diagram is presented in Figure 1. The study steering committee and study advisory committee comprised of investigators, patients, patient advocacy agencies, and third-party payer representatives developed and finalized the study protocol [20].

2.2 Eligibility Criteria and Study Screening

To be eligible for the study, participants must meet the following eligibility criteria at the screening visit: 1) men and women between 18 to 60 years of age, 2) established diagnosis of MS, as defined by the 2017 revision of McDonald Diagnostic Criteria [21], 3) RRMS disease course as defined by the 2013 revisions of the MS clinical course definition [22], 4) evidence of active disease based on: one or more MS relapses within the last 18 months prior to screening visit or radiological evidence of MS activity (≥2 new T2 lesions within the last 12 months from screening [compared to a previous recent MRI within 18 months of screening] or ≥1 gadolinium enhancing lesion (GdE) demonstrated on brain or spinal cord MRI performed within the last 12 months of screening), 5) ambulatory with disease onset ≤ 5 years and treatment-naïve (i.e., no MS DMT at any time in the past), 6) eligible to receive at least one form of DMT within each treatment arm and 7) Expanded Disability Status Scale (EDSS) at Baseline visit ≤ 6.5.

Exclusion criteria include 1) contraindications to all forms of DMT in either of the treatment arms, 2) prior treatment with any of the following medications: natalizumab, alemtuzumab, ocrelizumab, rituximab, cladribine, interferon beta- 1a, interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, daclizumab, mitoxantrone, 3) treatment with any of the following medications for reasons other than MS, in the last 12 months: cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, leflunomide, laquinimod, atacicept, other monoclonal antibodies, 4) clinically relevant medical or surgical conditions that, in the opinion of the investigator, would put the subject at risk by participating in the study, 5) inability to provide informed consent, 6) contraindication or inability to undergo MRI with Gd due to metal or metal implants, allergy to Gd contrast, claustrophobia, pain, spasticity, or excessive movement related to tremor, 7) unwillingness or inability to comply with the requirements of this protocol including the presence of any condition (physical, mental, or social) that, in the opinion of the investigator, is likely to affect the participant's ability to comply with the study protocol.

After providing written informed consent, participants complete screening procedures to confirm eligibility. After screening assessments are complete and all eligibility criteria is confirmed, participants are formally enrolled into the study.

2.3 Study Treatments

Early Highly Effective treatment arm

The EHT arm is one of the two randomized arms of the study and involves use of alemtuzumab, natalizumab, ocrelizumab, or rituximab as initial DMT. Once participants are randomized to the EHT arm, the choice of the specific DMT is made based on individual patient characteristics, by the patient, and the treating clinician in accordance with local guidelines. Participants starting EHT therapies may subsequently switch medications but are mostly expected to remain on these treatments for the duration of the study, based on described clinical experience [23–25].

Natalizumab treatment is used as described in prescribing information as 300 milligram (mg) intravenous infusion over one hour every four weeks. Alemtuzumab is used as approved as 12 mg/day administered by intravenous infusion for 2 treatment courses: first treatment course 12 mg/day on 5 consecutive days (60 mg total dose) and second treatment course 12 mg/day on 3 consecutive days (36 mg total dose) administered 12 months after the first treatment course. Ocrelizumab is used as approved by regulatory agencies, 600 mg by intravenous infusion every 24 weeks, administered as two 300 mg infusions on days 1 and 15 for the start dose and as a single 600 mg infusion thereafter. The regimen of rituximab includes two 1000 mg IV infusions separated by 2 weeks (one course) followed by 1000 mg every 6 months thereafter. In addition, lower doses of the medication can be used, both during the first treatment course and subsequent treatment courses including doses of 500 mg every 6 months or 1000 mg every 12 months.

Escalation Arm

The escalation arm involves use of any approved MS DMT, other than those described in EHT, as initial therapy with or without subsequent switch to any other approved treatment. Maintenance dosages used for the different initial escalation approaches include: glatiramer acetate (20 mg daily or 40 mg three times per week by subcutaneous [SC] injection); interferon beta-1a (22 or 44 microgram [mcg] SC three times per week); interferon beta-1a (30 mcg weekly intramuscular injection); interferon beta-1b (0.25 mg SC every other day); peginterferon beta-1a (125 mcg SC every 14 days); fingolimod (0.5 mg daily orally); teriflunomide (7 or 14 mg once daily orally); dimethyl fumarate (240 mg by mouth twice daily); cladribine (40-100 mg orally per treatment course); siponimod (1-2 mg daily orally after titration). We anticipate some participants will change therapy due to clinical activity, MRI activity, side effects, or convenience. Participants are allowed to switch, after receiving the initial dose, to any other approved therapies listed above at the discretion of the participant or the neurologist and in

addition may escalate to natalizumab, alemtuzumab, rituximab, ocrelizumab (at doses listed above), or mitoxantrone (12 mg/m^2 every 3 months IV, with cumulative dose limits and prior cardiac evaluation) per label indications. As new therapies become available, the steering committee will assign them to the EHT or escalation arm options.

Randomization

Patients will be randomized to the escalation or EHT arm 1:1 using minimisation. In minimisation the aim to minimize the imbalance between the number of patients in each treatment arm over multiple stratification variables. In DELIVER-MS minimisation will balance age and sex by site. Age will be grouped by tertiles (18-30, 31-36, 37-60) based on a normal distribution. Randomization using minimisation will be implemented via a web based system by a commercial provider, eResearch Technology Incorporated (ERT).

Observational Cohort

The emphasis of the study is to conduct a pragmatic randomized trial. Preparatory data collected for the DELIVER-MS study, previously published [20], indicated that a sizeable proportion of individuals would not be willing to be randomized. To provide additional data regarding the primary research question, participants who do not agree to randomization, or who agree to randomization but are not approved by insurance for coverage for a medication in the arm to which they were randomized despite appeal, are invited to participate in the observational cohort of the study. Participants in the observational study can use any treatment in the EHT or escalation arm at the discretion of the participant and treating clinicians. Participants may enroll directly into the observational cohort (excluding those who enter after randomization). In order to achieve balance between randomized and observational study components, sites are asked that the number of participants enrolled in the RCT should equal or exceed that in the observational study at all times. The observational cohort has the same

assessments as the randomized arms, both in terms of MRI and clinical testing. The goal of including an observational cohort is to ensure information on participants not willing to randomize or unable to start randomized medication is still collected and analyzed. The analysis in the observational study will focus on efficacy measures after minimizing treatment selection bias.

2.4 Study Schedule and Outcomes

Study visits include Screening (SC), Baseline (BL), and Months 6, 12, 24, and 36 visits. The full study schedule is presented in *Table 2*.

Windows for study visits include +/- 45 days, with the exception of the baseline visit, which will occur as close as possible prior to DMT start, after insurance approval of medication, and within 90 days of the screening visit. If the prospective participant has not initiated the prescribed medication by 90 days post-randomization, they are withdrawn from the study, unless prior approval from the study administrative team has been obtained, and would not be allowed to be re-screened for the study. Telephone calls are conducted at Months 3, 9, 15, 18, 21, 27, 30, and 33 +/-15 days.

<<TABLE 2 APPROXIMATELY HERE>>

Medical history, MS history, current MS symptoms, and eligibility are reviewed at the Screening Visit. Following confirmation of eligibility, participants are randomized and subsequently scheduled for the Baseline Visit once DMT approval is obtained and approximate start date for medication is known. Interval history, Adverse Event (AE) review, disease therapy review, concomitant therapy review, relapse review, and laboratory testing are conducted at Baseline and Months 3, 6, 9, 12, 15, 18, 24, 27, 30, 33, and 36. Vital signs, EDSS, MS Functional Composite (MSFC)-4 and PROs are obtained at Baseline and Months 12, 24, 36.

Brain MRI is obtained at Baseline (pre-treatment) and Months 6, 12, 24, and 36. The acquisition window for the baseline MRI is as close as possible prior to DMT start date and within 90 days of the screening visit. For scans other than baseline, the window for MRI is +/- 45 days of the clinical visit.

A repository of biosamples from participants is collected. Participation in the repository is optional for all participants. The purpose of the biorepository is so that biomarker discovery studies can be conducted after full enrollment into the trial to evaluate for predictors of longer-term disability and treatment response with the ultimate goal of individualizing treatment approaches in MS. Samples are collected at baseline and month 6 visits. Biosamples collected will include frozen serum, whole plasma for DNA, and peripheral blood mononuclear cells. Samples from US sites are shipped to, processed, and stored at the University of Alabama-Birmingham MS Center, in Birmingham, Alabama, US. Samples from UK sites are stored at the Welsh Neuroscience Research Tissue Bank, in Cardiff, Wales, UK.

2.5 Adverse event reporting

Reporting of these AEs will be conducted by the regular clinical provider for each participant as occurs in clinical practice. Because the study employs medications that are already approved, reporting of non-serious AEs is not being conducted, and there is no formal data safety monitoring board. Serious AEs are and AEs leading to treatment discontinuation are recorded in the study chart at the time of study visits and telephone visits. No formal reporting procedure to the FDA or health regulatory agencies is conducted within the contexts of the study.

Efficacy Assessments

Brain MRI

MRI is conducted using a predefined imaging protocol to include: localizer (<1 minute), 3D T1-weighted pre-contrast image such as Magnetization-Prepared Rapid Acquisition of Gradient

Echoes (MPRAGE) or Turbo Field Echo (TFE) with 1 mm isotropic resolution (approximately 5 minutes acquisition time), 3D T2 Fluid-Attenuated Inversion Recovery (FLAIR) 1 mm isotropic resolution (approximately 6 minutes acquisition time), 2D T2-weighted short and long dual-echo with 3-4mm slice thickness (approximately 3 minutes acquisition time), post-contrast T1-weighted image (approximately 5 minutes with delay). The type of Gd post contrast agent is at the discretion of the sites. The scan sequence was selected to be minimally complex, easy to acquire at all sites, and of short duration. MRI scanners and sequences are approved by the image analysis team at Cleveland Clinic. A dummy scan is completed at all sites prior to machine/sequence approval to troubleshoot any protocol problems.

Images are reported by a local radiologist according to routine clinical care. Image analysis is performed centrally at the Cleveland MRI Image Analysis Center and includes determination of baseline fractional brain volume (Brain Parenchymal Fraction [BPF] method with longitudinal changes determined using the Jacobian Integration (JI) method [26–28]. Other MRI measures include: GdE lesions (number, volume), T2-hyperintense lesions (N/E lesions, volume), T1-hypointense lesions (volume), and gray matter fraction.

Clinician-assessed measures of neurologic disability

The clinician-assessed measures of MS disease status listed below are used in this study at baseline and every 12 months including: 1) neurologic examination and calculation of functional system scales and EDSS, 2) MSFC-4 consisting of the Timed 25 foot walk [T25FW] (lower extremity function), 9 Hole Peg Test [9HPT] (upper extremity function), Symbol Digit Modalities Test [SDMT] (cognitive processing speed), and low contrast letter acuity (visual function). Relapse data (onset, duration, symptoms, and use of steroids) are captured at study visits retrospectively. Participants do not have unscheduled study visits to evaluate for potential relapses, as this was not the primary study outcome.

Patient-reported outcomes

The PROMs listed below are used in this study and are assessed at baseline and every 12 months: Multiple Sclerosis Impact Scale 29 (MSIS-29) [29], Patient Health Questionnaire (PHQ-8) [30], Neurological Quality of Life Scale (Neuro-QoL) short forms [31], and Treatment Satisfaction Questionnaire for Medication (TSQM) [32]. Treatment adherence and satisfaction are measured in addition to TSQM at Baseline and every 3 months with reports of percentage medication taken as scheduled.

3. Statistical Methods

3.1 Sample size calculation

The sample size was calculated based on the primary outcome measure of brain volume change, under the null hypothesis that escalation and EHT arms do not differ in relation to brain volume loss over the study period. Using published data from phase III trials published at the time of study design, we extracted a yearly brain volume change for each therapy. We then calculated yearly averages of brain volume loss for EHT treatments (natalizumab, alemtuzumab, rituximab, ocrelizumab), oral treatments (fingolimod, teriflunomide, dimethyl fumarate) and injectables (glatiramer, interferons). We used a standard deviation of 0.53, based on our image analysis laboratory's estimate incorporating clinical trial data and modern brain volume estimation techniques. We modeled the effect size for the EHT arm by using the EHT average over 3 years. For the escalation arm we modeled the first 2 years of treatment as 50% of participants using oral agents and 50% of patients using injectable agents. We modeled the third year of treatment as 60% of participants continuing with oral/injectable agents, and 40% escalating to EHT therapies (using the average effect of natalizumab, alemtuzumab, rituximab, ocrelizumab). This modeling was based on current US and UK practice for first-line therapies and an estimated 30% escalation rate to highly effective therapies (for a more conservative

sample size estimate, we used a 40% escalation in the third year of treatment). This resulted in an estimated annual brain volume loss of 0.442 in the escalation arm, and 0.282 in the EHT arm, over the course of 3 years.

Using the above estimated effects we conducted a sample size calculation based on a two sided t-test, a common standard deviation assumed to be 0.53 per year (based on the laquinimod versus interferon beta-1a vs. placebo study using JI), 80% power, and a 5% significance level. This requires 180 participants per group. Should 10% of participants drop out of the study or become lost to follow-up, 200 participants per group would be required.

3.2 Primary outcome analysis

The aim of this study is to test the effectiveness of EHT versus escalation treatment approaches with a primary outcome of brain volume loss from the baseline to Month 36. Analysis will be performed using a linear regression model, adjusting for treatment arm, age, sex, and baseline brain volume. The main result will be presented as the mean difference between treatment arms in the annualized percentage brain volume loss, along with a 95% confidence interval.

Brain volume loss as a short term outcome

Brain volume loss over three years was selected as the primary outcome for the study because it is meaningful to patients (as demonstrated in preparatory focus groups),[20] is feasible to be conducted in a 3-year multicenter study, and is the currently available measure most predictive of future MS-related disability. Volume loss shows good correlations with physical disability over both the short term[33] and long-term (Table 3). Brain volume loss also correlates with loss of cognitive function, an important feature of long-term disability in MS as well as with fatigue. Several studies have found that brain volume loss correlates cross-sectionally with cognitive measures including processing speed [34,35], verbal memory[36,37], and short term memory[38]. Brain volume also is predictive of future cognitive function, as well [39,40]. Physical

and cognitive fatigue are associated with brain volume loss [41,42]. Brain volume loss represents a meaningful and predictive outcome measure that is ideal as a global measure to compare DMT approaches. Brain volume loss rates across clinical trials are presented in Table 4.

<<TABLE 3-4 APPROXIMATELY HERE>>

3.3 Secondary outcome analysis

MRI secondary outcomes include 6 month to 36 month change in brain volume to account for pseudoatrophy effects. The main clinical secondary endpoint is the proportion of subjects with worsening on a multidimensional composite comprised of EDSS increase (>1.0 point or 1.5 points for those with EDSS of 0 at Baseline), 20% increase in T25FW, 20% increase in 9HPT, 10% decrease in SDMT, or 1-line decrease in LCLA confirmed over 12 months. This endpoint will be analyzed using a logistic regression model adjusting for treatment arm, age and sex. The results of our analyses will be adjusted odds ratios and 95% confidence intervals that indicate the effect of EHT vs. escalation arm on the outcome of interest. Baseline to Month 36 changes in the MSIS-29 and Neuro-QoL, the main secondary endpoint for PROs, will be analyzed using linear regression as described for the primary outcome. The secondary outcome regarding safety is a comparison of SAEs across the two treatment groups. This will be assessed in two ways. First, the percentage of participants who experience any SAE in each group will be compared using a chi-square test. Then, the rates of SAEs in each group will be compared using Poisson regressions. We also will compare the percentage of subjects with any SAE, CTCAE grade 3 and 4 AE, and AEs that lead to treatment discontinuation. Analysis will focus on all SAEs with a secondary analysis of treatment-related SAEs. Cumulative response of the TSQM pertaining to side-effects will be compared between EHT and escalation arms as well as individual therapies.

3.4 Exploratory outcome analyses

Additional exploratory outcomes include assessment of brain volume loss from Baseline to Month 12, Months 12 to 24, Months 12 to 36, and Months 24 to 36. This analysis will be conducted in a similar fashion to the primary outcome. We will also compare changes in T2 lesions volume, T1 hypointense lesion volume, and gray matter fraction using the same time points and analogous analyses.

3.5 Advisory Committee and Patient Engagement

An advisory committee was formed with stakeholders including people with MS, caregivers of people with MS, insurance industry representatives, health care agency regulators, advocacy group representatives (National Multiple Sclerosis Society, UK Multiple Sclerosis Society), and investigators. The advisory committee informs and guides the planning, conducting, and dissemination of the clinical trial. The advisory committee works closely with the steering committee (shared members from both committees) so that the advisory position strongly affects all study-related decisions.

4. Discussion

The DELIVER MS study seeks to answer an important question regarding the optimal approach to DMT use in early RRMS. MS is a common disease causing significant disability in young adults for which treatments are only partially effective. The study seeks to determine whether an EHT approach to DMT is more efficacious in preventing brain volume loss than an escalation approach. It is anticipated that results of the study will inform treatment decisions for MS patients. All participants will receive approved DMTs and, after the initial dose, will be allowed to change therapies (according to their licensed indication) at the discretion of the clinical neurologists and participants.

MS is a disease that starts as an inflammatory process in which immune cells infiltrate the CNS and destroy the myelin sheath surrounding neuronal cells. This demyelination, and the resulting neuroaxonal loss, is responsible for the physical symptoms of MS. The target of all MS DMT is by either decreasing the activity of the immune cells or by preventing them from infiltrating the CNS. The use of an escalation approach aims to maximize the safety of DMT. But this approach potentially puts patients at risk of incomplete control of disease activity, which may result in an increase in disability over time. The EHT approach aims to maximize efficacy early in the disease course but may have greater exposure to risk. The serious AEs associated with EHT DMTs occur in a small proportion of patients but may have high morbidity as illustrated with cases of progressive multifocal leukoencephalopathy, herpes infections, and atypical bacterial infections. However, several EHT options with a relatively safe profile do exist, including the use of natalizumab in JC virus seronegative patients, and the use of ocrelizumab or rituximab. The balance between the potential for DMT-associated AEs and the potential for disability accumulation as a result of incomplete disease control is a common discussion in the neurologist's office. A randomized study may limit this flexibility, but by randomizing to an approach patients and neurologists retain the ability to make decisions on individual therapies within medication groups. The options provided in this study for switching therapies as needed at the discretion of the participant and neurologist makes the study similar to routine clinical practice. We also selected inclusion criteria that allowed patients with a minimum of relapse (relapse within the last 18 months) and inflammatory activity (new T2 lesions/ gadolinium enhancing lesions within the last 12 months) so the study population was similar to patients newly starting DMTs in clinical practice.

There is currently no consensus on selection of initial DMTs. The comparative effectiveness and the long-term benefits of MS DMTs are currently unknown. We seek to study two different treatment algorithms, both commonly used in MS but that differ considerably. By comparing the

efficacy of two generic DMT algorithms, escalation vs EHT, we anticipate results that will be widely applicable to persons with MS. Some observational data also support the early use of EHT over escalation approaches [58]. Brain volume was selected as the outcome at 36 months, but long term plans will be put into place to follow patients in extension studies with follow-up of 5-10 years

DELIVER-MS is an international clinical trial. We considered it important to have representation of more than one country as prescribing practices might vary between North America and Europe. Although some regulatory hurdles needed to be overcome for an international study, we considered the effort a good investment for wider application of study results.

DELIVER-MS is also different to other MS DMT trials with both RCT and an observational study. The observational cohort is formed by participants not amenable to randomization, or who agree to randomization but are not approved for coverage for DMT coverage in the arm to which they were randomized, despite an appeal process. The observational cohort will be analyzed using propensity score adjustment based on baseline covariates with 1:1 matching adjustment. Although the RCT is the main study deliverable, the results of the observational arm and randomized arm will be compared and then the matched observational cohort and randomized cohort will be pooled for analysis. Further we will use a formal sensitivity analysis [59] to limit the degree of hidden bias that would be required to nullify significant conclusions from the matched analysis. We also note that the observational cohort is not a homogeneous sample and can be further divided for analyses into two subsamples as those participants eligible for the clinical trial who did not consent to randomization and those participants ineligible for the clinical trial due to lack of insurance approval. Therefore, we can perform appropriate pairwise comparisons of the three samples (clinical trial and two subsample observations cohorts) within each treatment arm on all outcomes of interest as well as appropriate pairwise comparisons of the three samples between treatment arms. Although the observational study will be informative to the population

not randomized, inherent biases in observational studies and inability to correct for unmeasured confounders may still exist.

We believe that the patient voice is crucial in reducing the unwarranted variation of MS treatment prescribing. Patient empowerment with educational approaches in conditions such as prostate cancer and benign prostatic hyperplasia has shown particular success in reducing unwarranted variation of prescribing. The current study will be conducted in adherence with engagement principles based on trust, respect, and transparency.[20] Patients with MS will be integral members of the research team and compensated for their time at fair market value. These patient partners will be involved in the planning, conduction, and results dissemination of the study. Training will be conducted in a bidirectional manner to ensure all team members improve both scientific knowledge and stakeholder perspectives. Bidirectional training includes training to the study investigators by stake holders and vice-versa. Training will ensure perspectives and rationale for all members of the advisory group are understood and addressed. During the study planning and execution, we will disseminate the current prescribing uncertainty to patients and their families. Our patient engagement team will liaise and coordinate their efforts with other stakeholders aiming to equip patients to ask more questions and to know more about what they might expect from their treatments.

The findings of this study will have an immediate impact on the management of MS internationally. The results will inform overall treatment philosophy and will guide both patients and clinicians in their decision making process. The study results are expected to impact the payers (insurance) and government agencies that decide on medication coverage.

Acknowledgements

Research reported in this work was funded through a Patient-Centered Outcomes Research Institute (PCORI) Award PCORI/MS-1610-37047, Daniel Ontaneda MD, Principal Investigator). All statements in this report are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee. Additional Support for DELIVER-MS is provided by the National Multiple Sclerosis Society and United Kingdom Multiple Sclerosis Society.

CRediT Author Statement

Daniel Ontaneda: conceptualization, data collection, writing- original draft preparation and editing, final assembly. **Emma C. Tallantyre**: conceptualization, data collection, writing- reviewing and editing. **Praneeta C. Raza:** writing-reviewing and editing. **Sarah M. Planchon:** conceptualization, data collection, writing- reviewing and editing. **Kunio Nakamura:** conceptualization, data collection, writing- reviewing and editing. **Deborah Miller:** conceptualization, writing- reviewing and editing. **Carrie Hersh:** conceptualization, writing- reviewing and editing. **Mathew Craner**: conceptualization, writing- reviewing and editing. **Clare Bale:** conceptualization, writing- reviewing and editing. **Burhan Chaudhry:** conceptualization, writing- reviewing and editing. **Douglas D Gunzler:** conceptualization, statistical analysis, writing- reviewing and editing. **Thomas E Love:** conceptualization, statistical analysis, writing- reviewing and editing. **Stephen Gerry:** conceptualization, statistical analysis, writing- reviewing and editing. **Alasdair Coles**: conceptualization, writing- reviewing and editing. **Jeffrey A. Cohen:** conceptualization, writing- reviewing and editing. **Nikos Evangelou:** conceptualization, data collection, writing- reviewing and editing.

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Table 1 Effect of approved disease modifying agents on relapse reduction rates and relative risks

Name	Route	Efficacy	Major Risks/Side Effects
Interferon Beta-1a	IM	32% reduction in Annual Relapse Rate (ARR) compared to placebo [6]	Flu-like side effects, injection site reactions, leukopenia, elevated liver enzymes, depression
Interferon Beta-1b	SC	34% reduction in ARR compared to placebo [7]	Flu-like side effects, injection site reactions, leukopenia, elevated liver enzymes, depression
Interferon Beta-1a	SC	32% reduction in ARR compared to placebo [8]	Flu-like side effects, injection site reactions, leukopenia, elevated liver enzymes, depression
Pegylated Interferon Beta-1a	SC	28% reduction in ARR compared to placebo [9]	Flu-like side effects, injection site reactions, leukopenia, elevated liver enzymes, depression
Glatiramer Acetate	SC	29% reduction in ARR compared to placebo [10]	Injection site reactions, immediate post-injection systemic reaction

Fingolimod	PO	54% reduction in ARR compared to placebo [11]	Cardiac events (bradycardia, atrio-ventricular block, cardiac arrest, arrhythmias), herpes infection, macular edema, elevated liver enzymes, lymphopenia
Teriflunomide	PO	31% reduction in ARR compared to placebo [12]	Teratogenesis, liver dysfunction, reactivation of latent tuberculosis, hair loss
Dimethyl Fumarate	PO	44-53% reduction in ARR compared to placebo[13], [14]	Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), flushing, lymphopenia
Daclizumab	SC	54% reduction in ARR compared to placebo [15]	Skin reactions, liver dysfunction, depression, infections
Cladribine	PO	58% reduction in ARR compared to placebo [16]	Lymphopenia, herpes zoster, teratogenesis.
Siponimod	PO	55% reduction in ARR compared to placebo in secondary progressive MS (SPMS)[17]	Lymphopenia, elevated liver enzymes, bradycardia, bradyarrhythmias), herpes infection, macular edema, seizures

HIGHLY EFFECTIVE			
Natalizumab	IV	68% reduction in ARR compared to placebo [18]	Infusion reactions, progressive multifocal leukoencephalopathy, lymphopenia, elevated liver enzymes, herpes simplex encephalitis
Alemtuzumab	IV	55% reduction in ARR compared to interferon beta-1a [19]	Infusion reactions, infections, autoimmune thrombocytopenia. autoimmune thyroid disease, autoimmune kidney disease
Ocrelizumab	IV	47% reduction in ARR compared to interferon beta-1a [20]	Infusion reactions, hypogammaglobulinemia
Intramuscular (IM), subcutaneous (SC), orally (PO), intravenous (IV)			

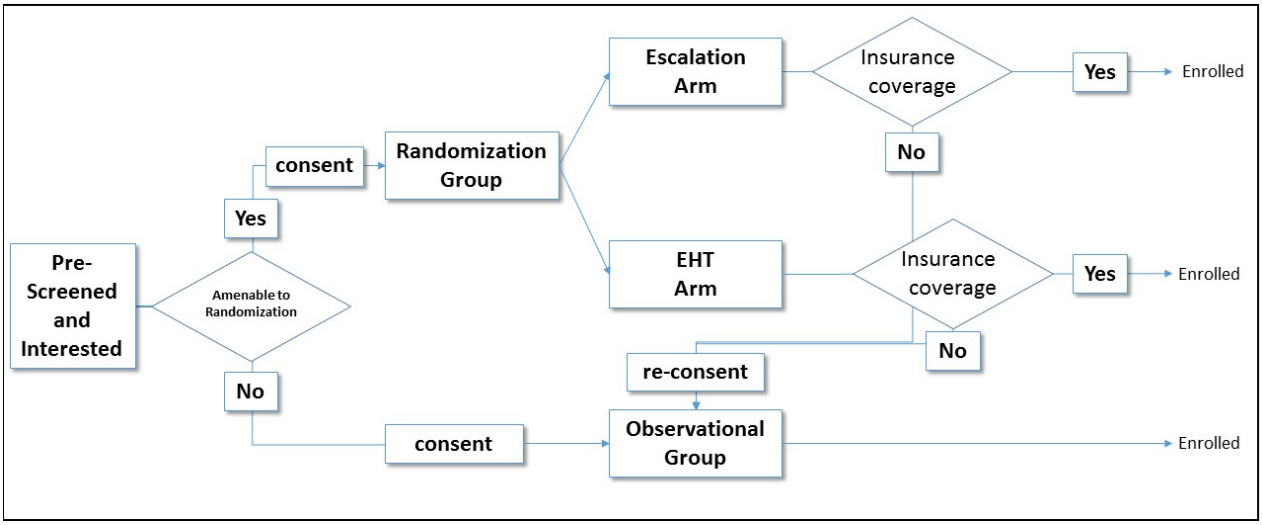
Table 2. Study Flow Chart						
	Visit 1	Visit 2	Visit 3,5, 7-9, 11-13	Visit 4	Visits 6,10,14	
Procedures	SC	BL	Telephone (Months 3, 9, 15, 18, 21, 27, 30, 33)	Office visit (Month 6)	Office visits (Months 12, 24, 36)	Early Withdrawal
Informed consent	X					
Eligibility criteria	X					
Medical, MS history	X					
Cohort Determination (RCT vs OBS)	X					
Randomization	X					
Interval history		X	X	X	X	X
Adverse Events review			X	X	X	X
Disease therapy review			X	X	X	X
Concomitant therapy review		X	X	X	X	X
Relapse review		X	X	X	X	X
Vital signs	X	X			X	X
EDSS	X	X			X	X
Multiple Sclerosis Functional Composite MSFC-4[1]		X			X	X
PRO[2]		X			X	X
Brain MRI		X		X	X	X
Lab testing review[3]	X	X	X	X	X	X
Biorepository blood sampling		X		X		

[1] MSFC-4 (Timed 25-Foot Walk T25FW, 9-Hole Peg Test 9HPT, Symbol Digit Modalities Test SDMT, low contrast letter acuity (LCLA),[2] Includes Multiple Sclerosis Impact Scale (MSIS-29), Patient Health Questionnaire 8 items (PHQ-8), Treatment Satisfaction Questionnaire for Medication(TSQM), Quality of Life in Neurological Disorders (Neuro-QoL) short forms, [3]May include recording of: complete blood count, metabolic panel, JC virus serology, Varicella zoster serology, interferon neutralizing antibodies, natalizumab neutralizing antibodies, rituximab neutralizing antibodies, immunoglobulin levels, CD19 counts, tuberculosis screening testing, thyroid function testing, urine analysis.

Table 3 Studies Showing Brain Volume Loss as a Predictor of Physical Disability			
Citation/Year	**Predictor/Time**	**Sample size**	**Software Method**
[42], 2015	EDSS confirmed disability progression over 4 years	3635	SIENA, SIENAX
[43], 2013	EDSS at 10 years	261	SIENA
[44], 2000	EDSS progression at 8 years	160	BPF
[45], 2010	Development of clinically definite MS	99	SIENA
[46], 2014	EDSS disease progression at 5/10 years	81	SIENA
[47], 2007	EDSS at 2 years	79	SIENA
[48], 2010	Increased EDSS at 5.5 years	54	SIENA
[49], 2003	EDSS over 4 years	38	Brain and lateral ventricle volumes
[50], 2012	EDSS disease progression at 7 years	27	SIENA

BPF = brain parenchymal fraction, EDSS – Expanded Disability Status Scale, SIENA = Secure Information Exchange Network Application

Figure 1: Flow chart for patients entering study



Abbreviations: EHT: early highly effective therapy