PROTOCOL TITLE: Teriflunomide (Aubagio®) Effects on Cognitive and Vocational Outcomes, as Related to Neurodegeneration in Multiple Sclerosis: A prospective, observational, single-blinded study.

INSTRUCTIONS: Complete Research Protocol (HRP-503)

- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable for the response. For example, most behavioral studies would answer all questions in section 30 with words to the effect of "drugs and medical devices are not used in this study."*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it will not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Include the full protocol title.

Teriflunomide (Aubagio®) Effects on Cognitive and Vocational Outcomes, as Related to Neurodegeneration in Multiple Sclerosis: A prospective, observational, single-blinded study.

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VERSION NUMBER:

Include the version number of this protocol.

Version 7.

DATE:

Include the date of submission or revision.

April 6, 2020

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Genzyme will financially support the work of the Investigator as it pertains to the conduct of this study.

Table of Contents

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

This is a prospective, observational, single-blinded, longitudinal study of terinflunomide effects on cognitive performance in patients with multiple sclerosis (MS) over 24 months. The primary aim of this study is to determine the effect of teriflunomide (Aubagio®) on cognitive abilities in patients with relapsing-remitting multiple sclerosis (RRMS). There are two secondary objectives, to [a] relate changes in cognition to vocational problems in employed participants, and [b] determine MRI correlates of change in cognition, more specifically gray-matter (GM) volume metrics, which we believe reflect neurodegeneration.

1.2 State the hypotheses to be tested.

Employed relapsing- remitting MS patients treated with teriflunomide (Aubagio®) are expected to follow a trajectory of cognitive performance and vocational stability over time, similar to that of healthy controls.

2.0 Background

2.1 Describe the relevant prior experience and gaps in current knowledge.

Cognitive Dysfunction in MS. Cognitive impairment constitutes a relevant clinical aspect of multiple sclerosis (MS). Depending on the disease phase and type, 40-65% of MS patients develop various degrees of cognitive dysfunction [1, 2]. These changes may begin very early in the disease process [3, 4]. Difficulties with learning and memory and slowed information processing speed, along with higher order functions such as abstraction, problem solving, and behavioral inhibition impact continued employment, daily function, and overall quality of life in MS [5-9].

Quantitative measurement of cognitive impairment in MS is frequently achieved through neuropsychological (NP) evaluation. These evaluations are conducted by highly trained specialists, using a variety of psychometrically robust measures [10, 11]. These measures are validated through extensive study of their relationships to clinically relevant phenomena such as employment status, functional independence, and progression as detected by MRI. Some examples of highly valid measures in MS are the Symbol Digit Modalities Test (SDMT) [12], Brief Visuospatial Memory Test- Revised (BVMT-R) [13], and Paced Auditory Serial Addition Test (PASAT) [14]. Relevance of these measures has been demonstrated by their relationship to deep gray matter and cortical atrophy [15, 16], as well as employment [11].

Cognitive Impairment and GM Atrophy in MS. MS is primarily a demyelinating disease of the central nervous system (CNS), but many patients also undergo progressive brain atrophy, especially in the gray matter (GM) [17-19]. GM atrophy plays a particularly prominent role in

MS cognitive decline [20-22]. White matter (WM) demyelination is also correlated with cognitive impairment [23] but in several studies comparing multiple measures, central atrophy or GM volume indices accounted for most variance in predicting cognitive impairment [24-27].

The paired thalamic nuclei are GM structures on both sides of the third ventricle and are involved in a wide range of neurological functions including motor, sensory, integrative, and higher cortical functions [28]. Thalamic location, unique neurologic functions, widespread cortical and subcortical connections and vulnerability to MS pathology from the earliest clinical disease stages [29-32] make it a critical structure for examining neurodegeneration [33, 34]. Given that progressive pathology of the thalamus has been shown in all different MS disease types [31, 32, 35-37] and that thalamic volume loss is detected in pediatric MS patients [38, 39], measurement of thalamic atrophy may be a useful outcome in MS clinical trials for the following reasons: a) meaningful change over time - thalamic atrophy develops more rapidly than whole brain, GM or WM atrophy [40, 41]; b) clinically meaningful change - in recent studies, thalamic atrophy was the one of MRI outcomes most significantly associated with development of clinically definite MS, not being free of clinical disease and having disability progression [40, 41]; c) detectable early in the disease - thalamic pathology was detected in CIS patients from the first onset of disease [40-42] and in early pediatric patients [43] and d) not affected by water fluid shifts - by its location and size, the thalamus is potentially less affected by the pseudoatrophy effect than other global or tissue-specific brain volume measures [28, 44]. All of this makes the measurement of thalamic atrophy an ideal candidate in future clinical trials, as recently suggested [28, 41]. However, the role of teriflunomide in slowing down thalamic atrophy progression is unknown.

MS studies focusing on deep GM and NP testing reveal robust correlation between thalamus volume and a range of cognitive tests. In one study [45] regression models controlling for the influence of third ventricle width, a proposed proxy for thalamus atrophy, also retained cortical GM regions in predicting performance on tests of memory and executive function. Likewise, thalamus and putamen volumes were retained in regression models predicting cognition, after accounting for cortical volume [24]. These studies lead us, and others [27, 30], to speculate that thalamus atrophy is an independent predictor of cognitive impairment, and is relevant in the progression of MS neurological disability in MS. The effect of teriflunomide on slowing down the progression of cognitive impairment in relapsing MS patients is unknown.

2.2 Describe any relevant preliminary data.

Cognition and Work Disability in MS. MS is commonly diagnosed in the third or fourth decade of life, in the prime of career development, thus greatly reducing lifetime achievement [46, 47]. Within five years of diagnosis half of individuals with MS have exited the work force and

within 15 years, two-thirds are unemployed [47]. Unemployment certainly impacts quality of life, both in terms of economic loss as well as lower self-esteem and risk of depression - work provides a sense of identity and has been found to improve long-term health [48] and quality of life [49].

Cognitive impairment is a chief driver of work disability in MS [50-52]. The problem is linked to underlying white matter demyelination, as well as progressive gray matter atrophy [17-19]. While studies show that cognitive impairment leads to work disability [50-53], most research employed a dichotomized outcome, designating patients as either employed or disabled. As noted in a recent topical review [54] this dichotomy misses more subtle work-related problems that impact patients prior to job loss.

There is considerable interest in improving clinical outcome measures in MS research. The PI, Dr. Benedict, is a board member of the NINDS Common Data Elements initiative [55], as well as the Multiple Sclerosis Outcome Assessments Consortium (MSOAC), a coalition of industry, academia, patient representatives, FDA, EMA, the Critical Path Institute, and the National MS Society [56]. He chaired the CDE cognition sub-committee that proposed optimal cognitive function metrics for MS research. The MSOAC will develop new standards for assessing outcomes in clinical trials of MS therapies. Dr. Benedict is also co-chair of the panel for the Brief International Cognitive Assessment in MS [57]. These initiatives highlight the relevance of cognition to patient care and outcomes in clinical trials, but as pointed out in a recent topical review, we lack understanding of when changes on NP outcomes become clinically meaningful [54].

Toward this end, we are pursuing MS vocational disability research with two objectives, one clinical, one methodological. First, our long-term goal is to track work-related problems more or less continuously so that transient problems can be identified by clinicians before patients lose work and incur other hardships. Second, by monitoring work status with more fine-tuned outcomes, we hope to correlate such changes with increments of change on NP metrics. Self-report surveys of work problems emphasizing self-appraisal have been developed [58]. Our approach is novel in that it is web-based, and emphasizes behaviorally-observed work events, not self-appraisal of capacity.

To lay the groundwork for the project, we have developed a web-based vocational monitoring survey called the MS Vocational Monitoring Survey (MSVMS) using the Vovici survey platform. The survey draws upon a variety of sources (e.g, the job accommodation network, National MS society, and current academic literature) for items that assess work events, vocational accommodations, and intervention strategies. Formats have been tested to minimize typing and computer functions that might be difficult for individuals with MS, and focus groups of MS patients

provided feedback on content and presentation. Approximately 49% of participants have taken the survey a second time, and 20% have taken it a third time. Feedback has been very positive, with some respondents expressing willingness to participate in subsequent phases of the research.

At the time of this writing we have enrolled approximately 250 patients in the program. In addition, we have just had a pilot study of 52 patients accepted for publication [59]. Participants were employed in a variety of professions/fields from the US, Canada, and UK. Many participants have reported work-related problems and/or receiving job accommodations, confirming the relevance of the proposed research. The patients completed the vocational web survey and a clinical assessment. Testing included the Timed 25 Foot Walk [T25FW] [60], Nine-Hole Peg Test [NHPT] [61], Beck Depression Inventory Fast Screen [BDIFS] [62] , California Verbal Learning Test, 2nd Edition [CVLT2] [63], Brief Visual Memory Test Revised [BVMTR] [13], Symbol Digit Modalities Test [SDMT] [64], and the Paced Auditory Serial Addition Test [PASAT] [14]. Thus, the exam spans the domains of ambulation, upper extremity motor function, cognition, and depression, not unlike the newer versions of the MSFC being proposed [65].

The mean number of hours worked per week was 36.7±8.3, range 08-60. Median annual salary was $45,000 USD. Participants were employed in a wide range of fields and job titles; the most common, teachers, professors, administrators, mechanics, bank tellers, and one police officer. No participant reported recent change in job title or requirements. Participants reported that they had held their current position for from 1 to 38 years (median 6 years). The majority (n=40) reported having disclosed to their employer having MS. The web survey also includes the MS Neuropsychological Screening Questionnaire (MSNQ) [66], and the mean MSNQ for the sample was 20.7±10.5.

Regarding negative work events, only 1 patient reported being formally disciplined by their employer. However, 5 reported verbal reprimands and 7 reported a decrease in scheduled work hours. Two patients reported diminution of job responsibilities and 4 had undergone mandated additional retraining.

Regarding accommodations, the majority of patients (n=34) did not report working extra hours at home in order to complete tasks or "catch-up," but the range of extra unpaid hours for the remaining 16 patients was from 2 to 20. Nine patients had been allowed flexible work hours. Among the more common specific accommodations were periodic rest breaks (n=4), additional time to complete tasks (n=4), and permission to work from home (n=8).

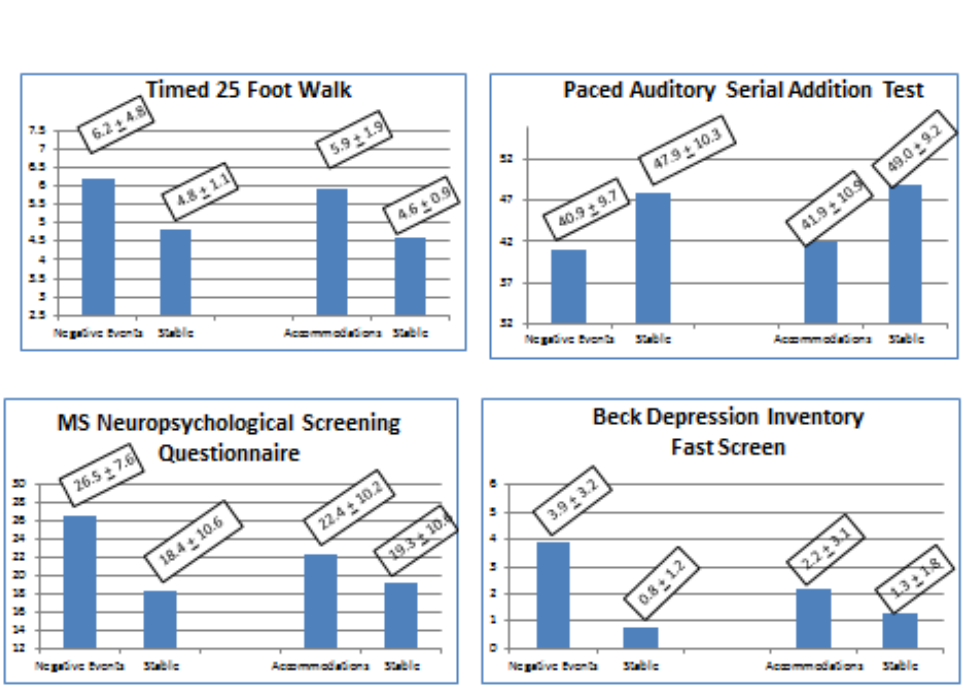
Logistic regression models were undertaken to determine which clinical factors are most predictive of vocational status. The model predicting negative work events [$R^2 = 0.54$] included PASAT [$B = -0.092$, $p = 0.026$]

and BDIFS [B = 0.814, p = 0.002], correctly classifying 81% of cases. The group means are presented in Figure 1. Patients reporting negative work events were found to have lower performance on PASAT and higher scores on the BDIFS. The effect size d for PASAT was 0.7 and for BDIFS was 1.4. The model predicting accommodations included PASAT [p = 0.032] and T25FW [p = 0.022], correctly classifying 70% of cases [R^2 = 0.30]. The model discriminating patients with decrease in scheduled work hours from normally scheduled counterparts retained [R^2 = 0.30] PASAT [p = 0.05] and BDIFS [p = 0.05], correctly classifying 90% of cases.

Figure 1. Sub-sample Means for Stable Patients vs Patients Reporting Negative Work Events and Accommodations.

MS patients were divided into two groups based on reports of negative work events and use of accommodations. Patients reporting no such events are categorized as stable.

Four domains of clinical status are assessed: ambulation = Timed 25 Foot Walk, cognition = Paced Auditory Serial Addition Test, patient reported neuropsychological symptoms = MS Neuropsychological Screening Questionnaire, depression = Beck Depression Inventory Fast Screen.



We believe that these preliminary results show that the proposed approach is feasible and valid. Now, we propose to combine this refined vocational status monitoring with an analysis of the effects of teriflunomide on cognition and MRI. Ralph H. B. Benedict, PhD, Professor in the UB Neurology Department, will serve as the Principal Investigator and will be responsible for directing the project.

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

The background clearly shows that MS cognitive dysfunction is common and is related to GM atrophy, and is a primary driver of work disability. However, we do not know how treatment with teriflunomide (Aubagio®) impacts GM atrophy and cognition, or how any hypothesized benefit would carry over to work capacity. We will address these questions in a sample of 30 relapsing MS patients treated with teriflunomide. The project will be carried out in conjunction with a concurrent study on MRI in teriflunomide treated patients (R Zivadinov, PI). An information processing speed index and a memory composite index will be calculated from conventional, validated neuropsychological tests as recommended by consensus opinion publications. Conventional clinical metrics for overall neurological disability will also be assessed. For working participants, vocational status will be monitored using a newly developed on line survey called the MS Vocational Monitoring Survey (MSVMS). Regional GM atrophy, as defined by measurement of thalamic and cortical atrophy, will serve as neurodegeneration outcomes. **We are not seeking funds to cover MRI acquisition or analysis, as this aspect of the study will be covered in Dr. Zivadinov's proposal**.

2.4 Include complete specific citations/references.

1. Rao SM, Leo GJ, Bernardin L, Unverzagt F: **Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction**. Neurology 1991, **41**:685-691.

2. Benedict RHB, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, Weinstock-Guttman B: **Validity of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS)**. Journal of the International Neuropsychological Society 2006, **12**:549-558.

3. Feuillet L, Reuter F, Audoin B, Malikova I, Barrau K, Cherif AA, Pelletier J: **Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis**. Mult Scler 2007, **13**(1):124-127.

4. Glanz BI, Holland CM, Gauthier SA, Amunwa EL, Liptak Z, Houtchens MK, Sperling RA, Khoury SJ, Guttmann CR, Weiner HL:

Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. Mult Scler 2007, **13**(8):1004-1010.

5. Simmons RD, Tribe KL, McDonald EA: **Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management**. Journal of Neurology 2010, **257**(6):926-936.

6. Benedict RHB, Zivadinov R: **Risk factors for and management of cognitive dysfunction in multiple sclerosis**. Nat Rev Neurol 2011, **7**(6):332-342.

7. Patti F, Pozzilli C, Montanari E, Pappalardo A, Piazza L, Levi A, Onesti E, Pesci I: **Effects of education level and employment status on HRQoL in early relapsing-remitting multiple sclerosis**. Mult Scler 2007, **13**(6):783-791.

8. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L: **Quality of life in multiple sclerosis: the impact of depression, fatigue and disability**. Multiple Sclerosis 2001, **7**(5):340-344.

9. Amato MP, Ponziani G, Siracusa G, Sorbi S: **Cognitive dysfunction in early-onset multiple sclerosis: a reappraisal after 10 years**. Archives of Neurology 2001, **58**(10):1602-1606.

10. Benedict RH, Fischer JS, Archibald CJ, Arnett PA, Beatty WW, Bobholz J, et al.: **Minimal Neuropsychological Assessment of MS Patients: A Consensus Approach**. Clinical Neuropsychologist 2002, **16**:381-397.

11. Benedict RH, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, Weinstock-Guttman B: **Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)**. J Int Neuropsychol Soc 2006, **12**(4):549-558.

12. Smith A: **Symbol digit modalities test: Manual**. Los Angeles: Western Psychological Services; 1982.

13. Benedict RHB: **Brief Visuospatial Memory Test - Revised: Professional Manual**. Odessa, Floriday: Psychological Assessment Resources, Inc.; 1997.

14. Gronwall D: **Paced auditory serial addition task: A measure of recovery from concussion**. Perceptual and Motor Skills 1977, **44**:367-373.

15. Benedict R, Ramasamy D, Munschauer FE, Weinstock-Guttman B, Zivadinov R: **Memory impairment in multiple sclerosis: correlation with deep gray matter and mesial temporal atrophy**. Multiple Sclerosis 2008, **14**:S252-S252.

16. Benedict RHB, Bruce J, Dwyer MG, Weinstock-Guttman B, Tjoa C, Tavazzi E, Munschauer FE, Zivadinov R: **Diffusion-weighted imaging**

predicts cognitive impairment in multiple sclerosis. Multiple Sclerosis 2007, **13**(6):722-730.

17. Geurts JJ, Stys PK, Minagar A, Amor S, Zivadinov R: **Gray matter pathology in (chronic) MS: modern views on an early observation**. J Neurol Sci 2009, **282**(1-2):12-20.

18. Hulst HE, Geurts JJ: **Gray matter imaging in multiple sclerosis: what have we learned?** BMC Neurol 2011, **11**:153.

19. Zivadinov R, Pirko I: **Advances in understanding gray matter pathology in multiple sclerosis: are we ready to redefine disease pathogenesis?** BMC Neurol 2012, **12**:9.

20. Benedict R, Bruce J, Dwyer M, Abderlahman N, Zivadinov R: **Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis.** Arch Neurol 2006, **63**(9):1301-1306.

21. Houtchens MK, Benedict RH, Killiany R, Sharma J, Jaisani Z, Singh B, Weinstock-Guttman B, Guttmann CR, Bakshi R: **Thalamic atrophy and cognition in multiple sclerosis**. Neurology 2007, **69**(12):1213-1223.

22. Roosendaal SD, Bendfeldt K, Vrenken H, Polman CH, Borgwardt S, Radue EW, Kappos L, Pelletier D, Hauser SL, Matthews PM et al: **Grey matter volume in a large cohort of MS patients: relation to MRI parameters and disability**. Mult Scler 2011, **17**(9):1098-1106.

23. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R: **Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis**. Neurology 2006, **66**(5):685-692.

24. Batista S, Zivadinov R, Hoogs M, Bergsland N, Heininen-Brown M, Dwyer MG, Weinstock-Guttman B, Benedict RH: **Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis**. J Neurol 2012, **259**(1):139-146.

25. Benedict RH, Ramasamy D, Munschauer F, Weinstock-Guttman B, Zivadinov R: **Memory impairment in multiple sclerosis: correlation with deep grey matter and mesial temporal atrophy**. J Neurol Neurosurg Psychiatry 2009, **80**(2):201-206.

26. Benedict RH, Zivadinov R: **Risk factors for and management of cognitive dysfunction in multiple sclerosis**. Nat Rev Neurol 2011, **7**(6):332-342.

27. Filippi M, Rocca MA, Benedict RH, DeLuca J, Geurts JJ, Rombouts SA, Ron M, Comi G: **The contribution of MRI in assessing cognitive impairment in multiple sclerosis**. Neurology 2010, **75**(23):2121-2128.

28. Minagar A, Barnett MH, Benedict RH, Pelletier D, Pirko I, Sahraian MA, Frohman E, Zivadinov R: **The thalamus and multiple**

sclerosis: Modern views on pathologic, imaging, and clinical aspects. Neurology 2013, **80**(2):210-219.

29. Calabrese M, Rinaldi F, Mattisi I, Bernardi V, Favaretto A, Perini P, Gallo P: **The predictive value of gray matter atrophy in clinically isolated syndromes**. Neurology 2011, **77**(3):257-263.

30. Henry RG, Shieh M, Amirbekian B, Chung S, Okuda DT, Pelletier D: **Connecting white matter injury and thalamic atrophy in clinically isolated syndromes**. J Neurol Sci 2009, **282**(1-2):61-66.

31. Henry RG, Shieh M, Okuda DT, Evangelista A, Gorno-Tempini ML, Pelletier D: **Regional Grey Matter Atrophy in Clinically Isolated Syndromes at Presentation**. J Neurol Neurosurg Psychiatry 2008, **79**(11):1236-1244.

32. Ramasamy DP, Benedict R, Cox JL, Fritz D, Abdelrahman N, Hussein S, Minagar A, Dwyer MG, Zivadinov R: **Extent of cerebellum, subcortical and cortical atrophy in patients with MS A case-control study**. J Neurol Sci 2009, **282**(1-2):47-54.

33. Cifelli A, Arridge M, Jezzard P, Esiri MM, Palace J, Matthews PM: **Thalamic neurodegeneration in multiple sclerosis**. Ann Neurol 2002, **52**(5):650-653.

34. Gilmore CP, Donaldson I, Bo L, Owens T, Lowe J, Evangelou N: **Regional variations in the extent and pattern of grey matter demyelination in multiple sclerosis: a comparison between the cerebral cortex, cerebellar cortex, deep grey matter nuclei and the spinal cord**. J Neurol Neurosurg Psychiatry 2009, **80**(2):182-187.

35. Bergsland N, Horakova D, Dwyer MG, Dolezal O, Seidl ZK, Vaneckova M, Krasensky J, Havrdova E, Zivadinov R: **Subcortical and Cortical Gray Matter Atrophy in a Large Sample of Patients with Clinically Isolated Syndrome and Early Relapsing-Remitting Multiple Sclerosis**. AJNR Am J Neuroradiol 2012.

36. Rocca MA, Mesaros S, Pagani E, Sormani MP, Comi G, Filippi M: **Thalamic damage and long-term progression of disability in multiple sclerosis**. Radiology 2010, **257**(2):463-469.

37. Mesaros S, Rocca MA, Pagani E, Sormani MP, Petrolini M, Comi G, Filippi M: **Thalamic damage predicts the evolution of primary-progressive multiple sclerosis at 5 years**. AJNR Am J Neuroradiol 2011, **32**(6):1016-1020.

38. Mesaros S, Rocca MA, Absinta M, Ghezzi A, Milani N, Moiola L, Veggiotti P, Comi G, Filippi M: **Evidence of thalamic gray matter loss in pediatric multiple sclerosis**. Neurology 2008, **70**(13):1107-1112.

39. Aubert-Broche B, Fonov V, Ghassemi R, Narayanan S, Arnold DL, Banwell B, Sled JG, Collins DL: **Regional brain atrophy in children with multiple sclerosis**. Neuroimage 2011, **58**(2):409-415.

40. Zivadinov R, Bergsland N, Dolezal O, Hussein S, Seidl Z, Dwyer M, Vaneckova M, Krasensky J, Potts J, Kalincik T et al: **Evolution of cortical and thalamus atrophy and disability progression in early RRMS over 5 years**. AJNR Am J Neuroradiol in press.

41. Zivadinov R, Havrdová E, Bergsland N, Tyblova M, Hagemeier J, Seidl Z, Dwyer M, Vaneckova M, Krasensky J, Carl E et al: **Thalamic atrophy is associated with development of clinically definite MS**. Radiology in press.

42. Hagemeier J, Weinstock-Guttman B, Bergsland N, Heininen-Brown M, Carl E, Kennedy C, Magnano C, Hojnacki D, Dwyer MG, Zivadinov R: **Iron Deposition on SWI-Filtered Phase in the Subcortical Deep Gray Matter of Patients with Clinically Isolated Syndrome May Precede Structure-Specific Atrophy**. AJNR Am J Neuroradiol 2012, **33**(8):1596-1601.

43. Hagemeier J, Yeh EA, Brown MH, Bergsland N, Dwyer MG, Carl E, Weinstock-Guttman B, Zivadinov R: **Iron content of the pulvinar nucleus of the thalamus is increased in adolescent multiple sclerosis**. Mult Scler 2012.

44. Zivadinov R, Reder A, Filippi M, Minagar A, Stüve O, Lassmann H, Racke M, Dwyer M, Frohman E, O. K: **Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis.** Neurology 2008, **71**:136-144.

45. Tekok-Kilic A, Benedict RH, Weinstock-Guttman B, Dwyer MG, Carone D, Srinivasaraghavan B, Yella V, Abdelrahman N, Munschauer F, Bakshi R et al: **Independent contributions of cortical gray matter atrophy and ventricle enlargement for predicting neuropsychological impairment in multiple sclerosis**. Neuroimage 2007, **36**:1294-1130.

46. Johnson KL, Amtmann D, Klasner ER, Kuehn CM, Yorkston KM: **Medical, pyschological, social, and programmatic barriers to employment for people with multiple sclerosis**. The Journal of Rehabilitation 2004, **70**(1):38+.

47. Uccelli MM, Specchia C, Battaglia MA, Miller DM: **Factors that influence the employment status of people with multiple sclerosis: a multi-national study**. Journal Of Neurology 2009, **256**(12):1989-1996.

48. Sweetland J, Riazi A, Cano SJ, Playford ED: **Vocational rehabilitation services for people with multiple sclerosis: what patients want from clinicians and employers**. Multiple Sclerosis Journal 2007, **13**(9):1183-1189.

49. Rumrill PD, Jr, Roessler RT, Fitzgerald SM: **Vocational rehabilitation-related predictors of quality of life among people with multiple sclerosis**. Journal of Vocational Rehabilitation 2004, **20**(3):155-163.

50. Beatty WW, Blanco CR, Wilbanks SL, Paul RH: **Demographic, clinical, and cognitive characteristics of multiple sclerosis patients who continue to work**. Journal of Neurologic Rehabilitation 1995, **9**:167-173.

51. Rao SM, Leo GJ, Ellington L, Nauertz T, Bernardin L, Unveragt F: **Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning**. Neurology 1991, **41**:692-696.

52. Benedict RHB, Wahlig E, Bakshi R, Fishman I, Munschauer F, Zivadinov R, Weinstock-Guttman B: **Predicting quality of life in multiple sclerosis: Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change**. Journal of the Neurological Sciences 2005:29-34.

53. Strober LB, Christodoulou C, Benedict RH, Westervelt HJ, Melville P, Scherl WF, Weinstock-Guttman B, Rizvi S, Goodman AD, Krupp LB: **Unemployment in multiple sclerosis: the contribution of personality and disease**. Mult Scler 2012, **18**(5):647-653.

54. Benedict RH, Walton MK: **Evaluating cognitive outcome measures for MS clinical trials: what is a clinically meaningful change?** Mult Scler 2012.

55. Benedict RHB, Krupp L, Francis G, Rao S, LaRocca N, Langdon D: **NINDS Common Data Elements, Multiple Sclerosis, Neuropsychology/Cognition Recommendations**. In. Edited by Group MCW. Washington: National Institute for Neurological Diseases and Stroke; 2012.

56. Cohen JA, Reingold SC, Polman CH, Wolinsky JS, MS IACoCTi: **Disability outcome measures in multiple sclerosis clinical trials: current status and future prospects**. Lancet 2012, **in press**.

57. Benedict R, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, Hamalainen P, Hartung H, Krupp L, Penner I et al: **Brief International Cognitive Assessment for MS (BICAMS): international standards for validation**. BMC Neurol 2012, **12**(1):55.

58. Honan CA, Brown RF, Hine DW, Vowels L, Wollin JA, Simmons RD, Pollard JD: **The multiple sclerosis work difficulties questionnaire**. Mult Scler 2012, **18**(6):871-880.

59. Benedict RHB, Rodgers JD, Emmert N, Kininger R, Weinstock Guttman B: **Negative Work Events and Accommodations in Employed Multiple Sclerosis Patients**. Multiple Sclerosis Journal, **in press**.

60. Schwid SR, Goodman AD, Mattson DH, Mihai C, Donohoe KM, Petrie MD, Scheid EA, Dudman JT, McDermott MP: **The measurement of ambulatory impairment in multiple sclerosis**. Neurology 1997, **49**(5):1419-1424.

61. Mathiowetz V, Weber K, Kashman N, Volland G: **Adult Norms for the Nine Hole Peg Test of Finger Dexterity**. Occupational Therapy Journal of Research 1985, **5**:24-38.

62. Beck AT, Steer RA, Brown GK: **BDI-Fast Screen for Medical Patients: Manual**. San Antonio, TX: Psychological Corporation; 2000.

63. Delis DC, Kramer JH, Kaplan E, Ober BA: **California Verbal Learning Test: Adult version**. San Antonio, TX: Psychological Corporation; 2000.

64. Smith A: **Symbol Digit Modalities Test (SDMT) manual (revised)**. Los Angeles: Western Psychological Services; 1982.

65. Ontaneda D, LaRocca N, Coetzee T, Rudick R, Force NMT: **Revisiting the multiple sclerosis functional composite: proceedings from the National Multiple Sclerosis Society (NMSS) Task Force on Clinical Disability Measures**. Mult Scler 2012, **18**(8):1074-1080.

66. Benedict RHB, Cox D, Thompson LL, Foley FW, Weinstock-Guttman B, Munschauer F: **Reliable screening for neuropsychological impairment in MS**. Multiple Sclerosis 2004, **10**:675-678.

67. Freeman JA, Hobart JC, Thompson AJ: **Does adding MS-specific items to a generic measure (the SF-36) improve measurement?** Neurology 2001, **57**(1):68-74.

68. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD: **The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus**. Archives of Neurology 1989, **46**(10):1121-1123.

69. Delis DC, Kaplan E, Kramer JH: **Delis-Kaplan Executive Function System**. San Antonio, Texas: Psychological Corporation; 2001.

70. Zivadinov R, Heininen-Brown M, Schirda CV, Poloni GU, Bergsland N, Magnano CR, Durfee J, Kennedy C, Carl E, Hagemeier J et al: **Abnormal subcortical deep-gray matter susceptibility-weighted imaging filtered phase measurements in patients with multiple sclerosis: a case-control study**. Neuroimage 2012, **59**(1):331-339.

71. Patenaude B, Smith SM, Kennedy DN, Jenkinson M: **A Bayesian model of shape and appearance for subcortical brain segmentation**. Neuroimage 2011, **56**(3):907-922.

72. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, De Stefano N: **Accurate, robust, and automated longitudinal and cross-sectional brain change analysis**. Neuroimage 2002, **17**(1):479-489.

73. Zhang Y, Brady M, Smith S: **Segmentation of brain MR images through a hidden Markov random field model and the expectation-**

maximization algorithm. IEEE transactions on medical imaging 2001, **20**(1):45-57.

74. Zivadinov R, Rudick RA, De Masi R, Nasuelli D, Ukmar M, Pozzi-Mucelli RS, Grop A, Cazzato G, Zorzon M: **Effects of IV methylprednisolone on brain atrophy in relapsing-remitting MS**. Neurology 2001, **57**(7):1239-1247.

75. Jenkinson M, Bannister P, Brady M, Smith S: **Improved optimization for the robust and accurate linear registration and motion correction of brain images**. Neuroimage 2002, **17**(2):825-841.

3.0 Inclusion and Exclusion Criteria

3.1 Describe the criteria that define who will be included or excluded in your final study sample.

We will enroll 30 relapsing MS patients new to teriflunomide therapy. We will also sample 30 healthy control volunteers, matched on demographics with the treated group.

We will include only MS subjects with a relapsing form of MS and who are enrolled in a research study that provides the Brain MRI metrics needed for GM atrophy analysis. Specific entrance criteria are as follows:

Inclusion criteria:

- Patient diagnosed with MS according to McDonald criteria
- Age 18-60
- Have a relapsing disease course
- Have EDSS scores 0-6.5
- Have a disease duration <20 years
- Treatment naïve to teriflunomide
- Willing and able to comply with the study procedures for the duration of the trial
- Have given written informed consent and signed Health Insurance Portability and Accountability Act (HIPAA) Authorization before any study-related activities are carried out
- Normal kidney functioning (creatinine clearance >59)
- None of the exclusion criteria

Exclusion criteria:

- MS patients with hepatic impairment
- Nursing mothers or pregnant women who will need to undergo 12 months follow-up

- Women of childbearing potential not using reliable contraception
- Patients currently treated with teriflunomide
- A clinically significant infectious or neurological (for HC only) illness (e.g., cellulitis, abscess, pneumonia, septicemia) within 30 days prior to treatment assignment
- Unwillingness or inability to comply with the requirements of this protocol including the presence of any condition (physical, mental, or social) that is likely to affect the subject's ability to comply with the study protocol
- History of neurological disorder other than MS
- History of developmental learning disorder or other developmental anomaly
- History of major depressive disorder, or other psychiatric disorder that could impact cognitive capacity, preceding diagnosis of MS
- Current major depressive episode
- Other pathology related to MRI abnormalities

Healthy Controls will be recruited if they are matched to the MS group on demographic variables, specifically age, achieved education level, gender and race. Controls will have no history of any neurologic or psychiatric disorder that could significantly influence cognitive capacity, including, but not limited to traumatic brain injury, schizophrenia, major depressive disorder, systemic lupus erythematosus, treatment with chemotherapy, mild cognitive impairment, and cerebrovascular disease.

3.2 Describe how individuals will be screened for eligibility.

Subjects will undergo eligibility screening conducted by trained members of the research team using the attached phone and in-person script, and health and social history form to determine whether the subject meet all of the eligibility criteria outlined above.

Please see attached.

3.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

- Inclusion criteria state subjects must be willing and able to comply with study procedures for the duration of the study.
- Individuals under the age of 18 will not be included
- Pregnant women will not be included
- Prisoners will not be included

3.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

We will not be including non-English speaking individuals. All neuropsychological measures are given in English and have not yet been translated.

4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

N/A

5.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

5.1 Describe when, where, and how potential subjects will be recruited.

N/A

5.2 Describe the methods that will be used to identify potential subjects.

N/A

5.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements

are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

N/A

6.0 Multi-Site Research (Multisite/Multicenter Only)

6.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

N/A

6.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

N/A

7.0 Study Timelines

7.1 Describe the duration of an individual subject's participation in the study.

This is a prospective, observational, single-blinded, longitudinal study of teriflunomide effects on cognitive performance and vocational status. Neuropsychological and MS outcome measures will be assessed at baseline (0 months), 12 months and 24 months. For those who are working, vocational status will be assessed every three months. The duration of participation in this study will be 2 years (24 months).

7.2 Describe the duration anticipated to enroll all study subjects.

Enrollment of all study subjects is expected to take 4 years (48 months).

7.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Completion of this study, including primary analyses is expected to be in 5 years.

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Primary Endpoints

- Information Processing Speed Index, mean z score based on previously published normative data.
- Memory Index, representing a mean z score including the CVLT2 and BVMTR, using previously published normative data.
- Executive Function Index, the mean z score obtained from the DKEFS Sorting Test, using previously published normative data.
- Frequencies of employed/unemployed status, negative work events and accommodations obtained from the Vocational Monitoring Survey.

Secondary Endpoints

Secondary endpoints will include other clinical metrics and MS outcome measure such as: EDSS, BDIFS, FSS, T25FW, 9HPT, MSNQ, and SF-36.

California Verbal Learning Test, second edition (CVLT-II)	New Learning & Memory	(D. C. Delis, Kramer, Kaplan, & Ober, 2000)	Patients listen to a list of words and are asked to recall them at different times (immediate and delayed recall) and recognize them at time of delayed recall.
Brief Visuospatial Memory Test-Revised (BVMTR)	New Learning & Memory	(R.H. Benedict, 1997)	Patients recall abstract visual displays at different times (immediate and delayed recall) and recognize them at time of delayed recall.
Paced Auditory Serial Addition Test (PASAT)	Processing Speed & Working Memory	(Gronwall, 1977)	Two 60-part trials are presented in 3-s and 2-s intervals wherein patients must continue to add consecutive integers

			to the preceding integer.
Symbol Digit Modalities Test (SDMT)	Processing Speed & Working Memory	(Smith, 1982)	Patients state numbers that correspond to matching symbols as they progress through multiple rows for 90-s.
Delis-Kaplan Executive Function System Sorting Test (DKEFS)	Executive Function	(D. C. Delis, Kaplan, & Kramer, 2001)	Patient repeatedly sort cards into two groups and describe their reasoning for the sorts.

8.2 Describe any primary or secondary safety endpoints.

N/A

9.0 Procedures Involved

9.1 Describe and explain the study design.

This is a prospective, observational, single-blinded, longitudinal study of teriflunomide effects on cognitive performance and vocational status. Neuropsychological, MRI (through another study) and MS outcome measures will be assessed at baseline (0 months), 12 months and 24 months. Vocational status will be assessed every three months. The duration of participation in this study will be 2 years (24 months).

Table 1. Proposed Assessments

EDSS	x				x				x
SDMT	x				x				x
PASAT	x				x				x
CVLT2	x				x				x
BVMTR	x				x				x
DKEFS	x				x				x
MSFC	x				x				x
BDIFS	x				x				x
FSS	x				x				x
SF36	x				x				x
MSNQ	x				x				x
Vocational Monitoring	x	x	x	x	x	x	x	x	x
MRI	x				x				x
	0	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
					Month				

Abbreviations:

EDSS = Expanded Disability Status Scale

SDMT = Symbol Digit Modalities Test

PASAT = Paced Auditory Serial Addition Test

CVLT2 = California Verbal Learning Test Second Edition

DKEFS = Delis Kaplan Executive Function System

MSFC = MS Functional Composite

BDIFS = Beck Depression Inventory Fast Screen

FSS = Fatigue Severity Scale

SF36 = Short Form 36

MSNQ = MS Neuropsychological Screening Questionnaire

9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Please see table above for a summary of the study procedures. During routine clinic visits, patients for whom terifunomide has been prescribed by a treating clinician will be referred to the study team for screening. Suitable candidates will be asked to provide informed consent prior to the Baseline (Month 0) study assessment. As shown below, all measures will be applied at this baseline assessment. The full evaluation will be repeated at one- and two-years. At each time point, subjects will be directed to the web-based survey.

Participants will complete approximately 75 minutes of clinical testing, as follows: The Expanded Disability Status Scale (EDSS) will be administered at baseline by a board certified clinical neurologist or study nurse for MS patients.

The clinical status of each patient will be further assessed using validated tools for motor function, mood, fatigue and cognitive capacity. Motor function tests will be the Timed 25 Foot Walk (T25FW) and the Nine-Hole Peg Test (NHPT). The Beck Depression Inventory Fast Screen for Medical Patients (BDIFS) will be used to measure the degree of depression. The Short Form 36 and the Fatigue Severity Scale (FSS) will be administered for QoL and fatigue respectively.

We will employ gold-standard measures of cognitive function as in our previous studies. The NP tests will include the California Verbal Learning Test, 2nd Edition [CVLT2], Sorting Test from the Delis-Kaplan Executive

Function System (DKEFS), Brief Visual Memory Test Revised [BVMTR], Symbol Digit Modalities Test [SDMT], and the Paced Auditory Serial Addition Test [PASAT]. The MS Neuropsychological Screening Questionnaire [MSNQ] will again be administered for patient reported neuropsychological symptoms. Alternate test forms will be applied as in our prior work with this battery in order to mitigate learning/practice effects.

Note that MRI procedures and costs will be funded by another research study. Healthy controls undergo the same study procedures, with the exception of clinical assessment prior to screening.

9.3 Describe procedures performed to lessen the probability or magnitude of risks.

Safety and Dosing Regimen:

This is an observational study following patients starting treatment with teriflunomide. Clinical and physical assessments will occur at baseline, 12 months and 24 months. We will evaluate occurrence of relapses and all patients will be monitored as per teriflunomide PI recommendations. All serious adverse events will be reported to Genzyme and local IRB within required timelines. The study protocol will be approved by the local Health Sciences Institutional Review Board at the University at Buffalo.

All relapsing MS patients who fulfill inclusion criteria will start teriflunomide at a dose of 14mg orally once daily and followed as per teriflunomide and clinician recommendations. The drug is not provided by the study.

Treatment for relapses or other conditions will be used at the discretion of the treating physician as deemed necessary for the management of the subject. All patients will be treated with 3-5g of methylprednisolone for the relapse and MRI will be performed (through a separate study) at least 30 days after steroid administration.

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue is not restricted but should be optimized as early as possible before the first dose of teriflunomide in an attempt to maintain consistent treatment for the duration of the study. Again, this is at the treating clinician's discretion and any such treatments are not covered by the study.

All patients will start the treatment at baseline, with teriflunomide adjustments in patients showing lack of treatment effect during the study. This will be made according to patient/physician decisions.

ALL decisions are to be made by the treating clinician. This study is observational. No drug is provided, no intervention is involved, and no clinical decisions are made by anyone other than the patient's treating clinician.

9.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Teriflunomide (Aubagio) is an oral disease-modifying drug used to treat relapsing forms of Multiple Sclerosis. This study will seek to determine the effects of teriflunomide on cognitive tests assessing information processing speed, memory, and executive function as well as determining if teriflunomide is protective for work disability in MS.

This drug is not provided as part of the study.

9.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Source records include:

- Expanded Disability Status Scale (EDSS)
- Symbol Digit Modalities Test (SDMT)
- Paced Auditory Serial Addition Test (PASAT)
- California Verbal Learning Test Second Edition (CVLT2)
- Brief Visuospatial Memory Test- Revised (BVMT-R)
- Delis Kaplan Executive Function System (DKEFS)
- MS Functional Composite (MSFC)
- Beck Depression Inventory Fast Screen (BDIFS)
- Fatigue Severity Scale (FSS)
- Short Form 36 (SF36)
- MS Neuropsychological Screening Questionnaire (MSNQ)
- Vocational Accommodations and Multiple Sclerosis Survey

Distribution of test forms is discouraged as per copyright regulations.

The script used to introduce the study to subjects is attached.

9.6 What data will be collected including long-term follow-up.

The above mentioned data will be collected at month 0, 12 and 24 with the exception of the vocational and multiple sclerosis survey for which data will be collected every 3 months.

9.7 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

N/A

10.0 Data and Specimen Banking

10.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.

Online survey responses will be stored online in a password-protected database. Neuropsychological testing data and clinical outcome measures will be stored in a locked cabinet until it has been entered into the database, after which it will be scanned into a pdf document and stored in a password protected online data storing system and the physical copies shredded. Digital files on the online server will only be able to be accessed bia encrypted lab computers with a security key. MRI data (from a separate study) will be kept in a password-protected database managed by co-investigator Dr. Zivadinov.

10.2 List the data to be stored or associated with each specimen.

Online survey data, Neuropsychological testing data, clinical outcome measures, and MRI data (from the separate study).

10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Identifiable data will not be released to any outside sources.

11.0 Data Management

11.1 Describe the data analysis plan, including any statistical procedures.

Statistical Plan:

Statistical analyses will be performed using SPSS 22.0 (IBM Inc., Armonk, NY, USA). Data will be analyzed on an intention-to-treat (ITT) basis. A p-value ≤ 0.05 will be used to determine significance.

We will compare the teriflunomide treated patients and controls on demographics, using the chi square test, Student's t-test and Mann-Whitney U test, as appropriate. Next the same approach will be pursued regarding the NP measures, controlling for demographics if necessary.

Within-group changes will be analyzed using repeated measures ANOVAs and ANCOVAs controlling for candidate covariates as may be found to be important via detailed analysis of correlation coefficients. Such incorporation of covariates will be approached conservatively due to the small sample size.

Cross-sectional analyses will investigate the degree to which MS patients are abnormal on vocational monitoring outcomes. Again, as above, the effects of teriflunomide in MS will be measured using repeated measures ANOVAs and ANCOVAs controlling for candidate covariates as may be found to be important via detailed analysis of correlation coefficients.

Within-patient changes from baseline MRI measures and statistical differences within groups will be calculated using the paired t-test or Wilcoxon-rank sum tests. Model assumptions of linearity, normality and homoschedasticity will be verified. Each of the MRI parameters will be examined and appropriate transformations will be applied, if necessary. Other group-wise comparisons will be made between MS patients and HC or MS patients who had MRI (new T2 and CE lesions) or both clinical (relapse) and MRI activity.

This is an exploratory study on the effects of teriflunomide on work status and cognition in MS and no previous data are available for the repeated measures analyses. For the cross-sectional analysis, we are powered to detect large effects. Because of this limitation in the sample size, we will emphasize the within-group analysis of the teriflunomide patient outcomes where we will have power to detect moderate effects.

11.2 Provide a power analysis.

N/A

11.3 Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Physical data protection: NP testing data will be maintained in locked filing cabinets within a locked room (4085) within UBMD Neurology at the Conventus Center, 1001 Main Street, Buffalo, NY 14203 until it has been entered into the database, at which time it will be scanned into a pdf document and stored in a password protected online data storing system and the physical copies shredded The NP testing database will be kept without identifying information on an encrypted computer and matched to online survey information using the assigned code number.

Online security: In order to maintain security of the information collected online, the researchers will use https://www.benedictneurocog.com and host the online survey. The website domain was purchased by the principal investigator of the study. Security will be maintained by enabling Secure Socket Layers (SSL) through the website, protecting the information passed between the survey and the researchers. This is the same security feature used for online marketing to protect sensitive information such as credit card information.

Offline data protection: Once retrieved from the www.benedictneurocog.com/ website the survey data will be separated from the contact and identifying information and maintained on separate encrypted computers. In addition, the survey responses will be purged from www.benedictneurocog.com/ servers in order to minimize any risk of online security being broken. Only a code number assigned by the researchers will be maintained as a link between the identifying information and the research responses. Other digital files (NP database and pdfs) on the online server will only be able to be accessed via encrypted lab computers with a security key.

Email security: All email correspondence will be conducted through the University at Buffalo email address mscogsur@buffalo.edu devoted specifically to the online survey project. This will ensure correspondence is maintained on a secure email server and is not mixed with personal correspondence.

11.4 Describe any procedures that will be used for quality control of collected data.

Scoring and data entry will be completed and checked by trained staff members.

11.5 Describe how data and specimens will be handled study-wide:

Neuropsychological testing data will be kept in a locked room and in a locked cabinet. After data scoring and entry, neuropsychological testing files will be de-identified by blacking out identification information, scanned into the online server, and the physical copies shredded. Databases with identifiable information will not be kept on personal computers and only stored online in a password protected website.

11.6 What information will be included in that data or associated with the specimens?

Data points related to information processing speed, memory, executive functioning, depression, fatigue, disability and vocational status.

11.7 Where and how data or specimens will be stored?

Online survey data will be stored in an online password protected file sharing system. Neuropsychological testing data will be kept in a locked room and in a locked cabinet;after they have been entered, they will be scanned into pdf files and uploaded to a secure, password protected server only able to be accessed by designated lab computers with a security key. Physical files will then be shredded after they have been uploaded to this server.

11.8 How long the data or specimens will be stored?

Electronic copies of data are maintained indefinitely. Physical copies of data are maintained until they have been entered into the database, after which they will be scanned into a pdf document and are then shredded. The digital pdf of the physical data will be maintained indefinitely on an encrypted server in password protected folders.

11.9 Who will have access to the data or specimens?

Trained staff under Dr. Ralph Benedict (Primary Investigator) directly involved in the conduct of this study will have access to data.

11.10 Who is responsible for receipt or transmission of the data or specimens?

N/A

11.11 How data and specimens will be transported?

N/A

12.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

12.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Participation in this study involves no more than minimal risk to participants.

In order to maintain patient quality of care, those participants reporting a raw score drop of more than 6 points in the online MSNQ (1/2 standard deviation) between one or more data points will be referred to the PI (a board certified neuropsychologist) for consultation with the potential of a recommendation to consult their neurologist if there are signs that the decline in MSNQ is the result of a current exacerbation.

Patients will also be assessed for general safety and asked about adverse events and medication changes during screening for Neuropsychological evaluations at month 0, 12, and 24. Any potential study-related issues and/or adverse events impacting a patient's health or well-being will be communicated to his or her clinician.

12.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

See 12.1

12.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Safety information will be collected at each study visit and via the online survey.

12.4 Describe the frequency of data collection, including when safety data collection starts.

Data for the vocational online survey will be collected for each patient at three-month intervals by sending a reminder email to take the survey from home.

Neuropsychological testing data will be collected at month 0, month 12, and month 24.

12.5 Describe who will review the data.

Designated, trained staff under Dr. Ralph Benedict (Primary Investigator) will review survey and neuropsychological data.

12.6 Describe the frequency or periodicity of review of cumulative data.

Review of online survey data will occur within one week of receipt of the survey response. Neuropsychological data will be reviewed at the initial scoring of neuropsychological tests conducted at each study visit and additionally if the need arises.

12.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

N/A

12.8 Describe any conditions that trigger an immediate suspension of the research.

N/A

13.0 Withdrawal of Subjects

13.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Circumstances that could possibly lead to the withdrawal of a subject without his or her consent would be if continuation of treatment with teriflunomide were no longer in the patient's best interest, based on his/her treating clinician's judgment. The treating clinician may remove subjects from the study at any time should he/she feel it is no longer in the subject's best interest. Healthy controls can be withdrawn from the study if they no longer wish to participate or if they are non-compliant with the study procedures.

13.2 Describe any procedures for orderly termination.

N/A

13.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Participation in this study is voluntary. Patients being treated with the study medication may refuse to participate without penalty and such refusal will not prejudice future treatment at theUBMD Neurology . If a

subject chooses to withdraw from the study, the data collected up to the time of withdrawal will continue to be used, but the subject will no longer be contacted and no further data will be collected. Healthy controls withdrawing from the study will not be penalized in any way.

14.0 Risks to Subjects

14.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

There are no identified risks to the subjects in this study. If participants should feel discomfort or choose not to answer a question they are free to discontinue the neuropsychological evaluation and/or surveys.

14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

N/A

14.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

N/A

14.4 If applicable, describe risks to others who are not subjects.

N/A

15.0 Potential Benefits to Subjects

15.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

There are no direct benefits to the participants in this study. The potential benefits to society are increased knowledge about the effects of teriflunomide on cognitive function and vocational status.

15.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

There are no direct benefits to the participants in this study.

16.0 Vulnerable Populations

16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

N/A

17.0 Community-Based Participatory Research

17.1 Describe involvement of the community in the design and conduct of the research.

N/A

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

18.0 Sharing of Results with Subjects

18.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Participants and/or clinicians requesting interpretation of neuropsychological testing will be referred for clinical consultation and evaluation with Dr. Ralph Benedict. If a patient reports adverse side effects of teriflunomide during a study visit, the PI and/or research personnel will notify the patient's neurologist.

19.0 Setting

19.1 Describe the sites or locations where your research team will conduct the research.

All research will be conducted at through the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203. Subjects may complete the online survey from their homes.

19.2 Identify where your research team will identify and recruit potential subjects.

All identification of potential subjects will be conducted at the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203, based on clinical referral.

Healthy controls will be identified from the community and around the medical campus via word of mouth. Participants will be also recruited via flyers posted in various locations on and around the Buffalo Medical Campus and community. Community locations will include grocery stores, coffee shops, libraries, and shopping malls. We will seek permission from individual sites in the community, as applicable, prior to posting of flyers.

We may utilize the services of The CTSI Community Engagement Team (CET) to assist in subject recruitment. Outreach also occurs from the CTSI Community Recruitment Liaison via email or postal mail with the IRB approved flyer for the study.

The CET also hosts a standing table at Conventus on the 4th floor of UBMD where the IRB approved flyer may be spotlighted, if deemed appropriate for this recruitment strategy, as well.

Please find attached flyer.

19.3 Identify where research procedures will be performed.

All research will be conducted at the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203. Subjects may complete the online survey from their homes.

19.4 Describe the composition and involvement of any community advisory board.

N/A

19.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

N/A

20.0 Resources Available

20.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

This study will be conducted and supervised by qualified investigators.

Dr. Ralph H B Benedict is the senior investigator and a board certified neuropsychologist. He holds the rank of professor in the Department of Neurology at the University at Buffalo, State University of New York. He is the lead neuropsychologist for the Jacobs MS Center, directed by Bianca Weinstock-Guttman, MD, who is also a contributor to this project.

All research staff involved in this research project must pass rigorous training on administering neuropsychological tests, patient interaction protocol and consent process protocol. Study coordinator is responsible for tracking referrals, recruitment, screening, consenting and monitoring patient progress over the course of their enrollment. All research staff has completed GRP training.

The PI will be responsible for coordinating the database, conducting statistical analyses, coordinating recruitment efforts and presenting the data.

Describe other resources available to conduct the research: For example, as appropriate:

20.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

On average 120 MS patients per week are seen at through the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203 . Approximately 5-10 patients are prescribed teriflunomide per month. We aim to recruit all patients who are prescribed teriflunomide meet screening criteria, and agree to participate.

20.3 Describe the time that you will devote to conducting and completing the research.

One full time research coordinator and two part time research coordinators will devote half of their time to conducting and completing the research.

20.4 Describe your facilities.

Our research is conducted through the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203 . All neuropsychological testing will be conducted in private rooms.

20.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

There are no anticipated consequences associated with this observational study. However, relapses or other conditions that may occur at some point during the study will be identified and treated by the clinician and at his/her discretion. No treatment or clinical care will be covered by the study.

20.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

All new staff will undergo research orientation and will not be cleared for research work until approved by the PI and research coordinator. All new staff must complete GRP and CITI training.

21.0 Prior Approvals

21.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

N/A

22.0 Recruitment Methods

22.1 Describe when, where, and how potential subjects will be recruited.

Subjects will be patients from the UBMD Department of Neurology/Jacobs MS Center in Buffalo, NY. Patients newly prescribed teriflunomide by their neurologists will be referred to research staff and then offered the opportunity to participate in the study. Research staff will then screen patients to determine eligibility for the study. Willing and eligible patients will provide informed consent prior to any research procedures.

Healthy controls may be recruited from family and friends of participating MS subjects, from the surrounding medical campus/community via word of mouth or via flyers. We may also utilize the services of The CTSI Community Engagement Team (CET) to assist in subject recruitment. The CET hosts the Buffalo Research Registry (BRR) that can connect us to community members who have completed a health profile and have agreed to be contacted about potential research opportunities that they may be an interested in based on their self-reported information. The CET also goes out and tables at many events in the community throughout the year and if and when it is appropriate they may have this studies IRB approved flyer spotlighted at the table. They attend events such as Good for the Neighborhood hosted by Independent Health Foundation, UB on the Green, Juneteenth, Elmwood Arts Festival and many others. Outreach occurs from the CTSI Community Recruitment Liaison via email or postal mail with the IRB approved flyer for the study. Then the BRR member can contact the coordinator (info provided on the IRB approved flyer) if they are interested. One week after outreach has been completed the Community Recruitment Liaison will give the matched BRR members contact info (name, phone, address and email) to the study coordinator so that they may conduct follow up to gauge interest in participation.

The CET also hosts a standing table at Conventus on the 4th floor of UBMD where the IRB approved flyer may be spotlighted, if deemed appropriate for this recruitment strategy, as well.

22.2 Describe the source of subjects.

Refer to 22.1

22.3 Describe the methods that will be used to identify potential subjects.

Refer to 22.1

22.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Please find attached flyer under recruitment materials.

22.5 Describe the amount and timing of any payments to subjects.

Subjects will receive a check for $125 after each neuropsychological assessment at months 0, 12, and 24.

23.0 Local Number of Subjects

23.1 Indicate the total number of subjects to be accrued locally.

All 30 MS patients and 30 healthy controls will be accrued locally.

23.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Subjects who agree to participate and pass screening requirements will be enrolled in the study. Thirty MS patients and 30 normal controls will be enrolled.

24.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

24.1 Where and how data or specimens will be stored locally?

Refer to 10.1

24.2 How long the data or specimens will be stored locally?

Data will be stored until completion of all study related activities

24.3 Who will have access to the data or specimens locally?

PI and research staff

24.4 Who is responsible for receipt or transmission of the data or specimens locally?

N/A

24.5 How data and specimens will be transported locally?

N/A

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

No information will be shared with outside sources. All data will be kept in a locked safe and/or stored in a password protected online data storing system.

25.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

All study participants will be adequately informed of the aims, methods, funding sources, anticipated benefits and potential risks of the study. The subject will be informed of the right to abstain or withdraw from participation in the study at any time without reprisal. After ensuring that the participant has understood the information, freely given informed consent will be obtained.

25.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Only trained and authorized staff will be granted access to data.

26.0 Compensation for Research-Related Injury

26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

N/A

26.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

N/A

27.0 Economic Burden to Subjects

27.1 Describe any costs that subjects may be responsible for because of participation in the research.

N/A

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent

Yes

28.2 Describe where the consent process take place

The consent process will take place in a private testing room.

28.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Patients are informed of study procedures when referred to research staff by their neurologists. Consent from all subjects is obtained prior to any procedures.

28.4 Describe any process to ensure ongoing consent.

Subject understanding of study objectives, procedures, potential risks/benefits, etc. will be ensured prior to enrollment and at the beginning of each subsequent study visit. Assent will be obtained. At each online survey assessment patients will be ask to give online consent.

28.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

We will be following the SOP: Informed Consent Process for Research (HRP-090).

Non-English Speaking Subjects

28.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

N/A

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

28.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

N/A

28.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

N/A

Subjects who are not yet adults (infants, children, teenagers)

28.10Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

N/A

28.11For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

N/A

28.12Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

N/A

28.13Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

N/A

28.14Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

N/A

28.15When assent of children is obtained describe whether and how it will be documented.

N/A

Cognitively Impaired Adults

28.16Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

N/A

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

28.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

N/A

28.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

N/A

28.19Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

N/A

28.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

N/A

29.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

29.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

We will be following the SOP: Written Documentation of Consent (HRP-091).

30.0 Drugs or Devices

30.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

N/A

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

30.2 Identify the holder of the IND/IDE/Abbreviated IDE.

N/A

30.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

N/A

31.0 Drugs or Devices

☒ **N/A:** This study does not involve drugs or devices. This section does not apply.

31.1 If the research involves drugs or devices, list and describe all drugs and devices used in the research, the purpose of their use, and their regulatory approval status.

Response:

31.2 *Describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

Response:

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

31.3 Identify the holder of the IND/IDE/Abbreviated IDE.

Response:

31.4 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response:

32.0 Humanitarian Use Devices

☒ **N/A:** This study does not involve humanitarian use devices. This does not apply.

32.1 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

32.2 For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.