Effects of Acthar on Recovery From Cognitive Relapses in MS
NCT02290444
Study Protocol
Document Revision Date: June 12, 2018
IRB Approval of Revision: July 30, 2018

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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.

Response: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

PRINCIPAL INVESTIGATOR:

Name
Department
Telephone Number
Email Address

Response:

Ralph HB Benedict

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Neurology

716-323-0556

Benedict@buffalo.edu

VERSION NUMBER:

Include the version number of this protocol.

Response: 4

DATE:

Include the date of submission or revision.

Response: June 12 2018

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.

Response:

This study is supported by Mallinckrodt Pharmaceuticals (formerly Questcor).

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Table of Contents

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

We propose to study the effect of Acthar® on recovery from cognitive relapses in multiple sclerosis (MS). Cognitive relapses are acute clinical declines in concentration, memory, working memory or increased fatigue.Cognitive relapses may also be detected by the presence on brain MRI of new active supratentorial Gad enhancing lesions. We will use well-validated, objective metrics to evaluate cognitive changes following treatment with a 5-day course of Acthar®over three months in patients showing cognitive relapses in MS. To account for the possible practice effects of cognitive testing over a three-month period, we will compare the results to a matched sample of MS patients who are clinically stable.

1.2 State the hypotheses to be tested.

The primary hypothesis of the study is that due to enhanced melanocortin response, Actharwill facilitate recovery from cognitive changes occurring during cognitively focused relapse, and that patients treated with Acthar will return to baseline following treatment.

2.0 Background

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

Multiple sclerosis (MS) is an auto-immune disease causing inflammatory and neurodegenerative processes within the central nervous system (CNS). Supratentorial CNS damage has been shown to relate to cognitive impairment.[1, 2] The most common courses of MS (relapsing-remitting [RR] & secondary-progressive [SP]) typically present as a series of acute exacerbations or 'relapses' wherein significant demyelination contributes to lesion activity and clinical changes, including cognitive deterioration.[3] While the rate of relapse is likely to decline over time in patients with secondary-progressive MS, relapses/exacerbations are not uncommon in this population.

Cognitiveimpairment 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. These changes may begin very early in the disease process.[4, 5] Difficulties with learning and memory and slowed information processing speed, along with difficulties in higher order functions such as abstraction, problem solving, and behavioral inhibition impact continued employment, daily function, and overall quality of life.[6-10]

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Quantitative measurement of cognitive impairment in MS is frequently through neuropsychological evaluation (NP). These evaluations are conducted by highly trained specialists, using a variety of psychometrically robust measures.[12, 13] These neuroperformancemeasures 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),[14] Brief Visualspatial Memory Test- Revised (BVMT-R),[15] and Paced Auditory Serial Addition Test (PASAT).[16] Relevance of these measures has been demonstrated by their relationship to cortical atrophy,[2, 17] employment,[13] and more common methods of clinical assessment such as walking speed and manual dexterity.[18]

While cognitive impairment over the span of the illness continues to be a focus of extensive research, few attempts have been made to study acute relapses with primarily cognitive sequelae (i.e., cognitive relapses).[3, 11] This is due to the considerable methodological difficulties involved in studying the phenomenon.

2.2 Describe any relevant preliminary data.

A current study from our group, nearing completion, has demonstrated a substantial change in neuropsychological (NP) measures in MS patients with cognitive relapses (Benedict, et al. In Press) following treatment with high dose IV corticosteroids. Corticosteroids have been shown to promote stabilization or improvement in randomized clinical trials following acute exacerbations[19] by reducing inflammation and possibly promoting re-myelination, though evidence for this is still being sought.[20, 21]Though infusion administered corticosteroids are now accepted as the standard of care in the treatment of MS exacerbations, they are not without side effects and many patients find the infusion route of administration intolerable. Alternate treatments, particularly those demonstrated to enhance recovery in functional domains, are vitally important.

ACTH has been used for decades to treat MS exacerbations. Recent data provides evidence that the beneficial effect of ACTH in other diseases (i.e. nephrotic syndrome, opsoclonus-myoclonus and infantile spasms) may be related not only to its direct induction of corticosteroid production, but also to a corticosteroid-independent melanocortin path.[22]Melanocortins have anti-inflammatory and possible neuroprotective effects and have been shown to improve attention, memory and learning. ACTH binding to central and peripheral melanocortin receptors downregulatesimmunocyte activity, an effect superimposed onto its

better known glucocorticoid-mediated actions. In addition, ACTH potentiates parasympathetic and SNS activity. Both lessen immune responsiveness,[22] and possibly provide neuroprotective effects.

In addition to its effectiveness in treating cognitive relapses and the neuroprotective factors tentatively associated with its administration, ACTH may not only enhance initial recovery, but it may also slow the long-term progression of cognitive impairment. Therefore, we propose to study the influence of Acthar on recovery from cognitive relapses in MS, and compare this to the influence of corticosteroid administration, as well as to stable MS patients.

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

Response: The relative frequency of cognitive relapses is unknown at this time, though the current study and past studies along the same lines are the first to work towards this identification. The measures mentioned above will be those used in identification of cognitive relapses when this topic is explored. There is limited evidence that certain neuropsychological deficits detected during an acute relapse may be reversible, particularly in patients who initially have mild cognitive impairment, with improvement being in part correlated with the reduction in acute lesion load.[3]

Both corticosteroids and adenocorticotropic hormone (Acthar) have been shown to promote stabilization or improvement in randomized clinical trials following acute exacerbations[19] by reducing inflammation and possibly promoting remyelination, though evidence for this is still being sought.[20, 21] IV Corticosteroids are typically the first choice for treatment, except in the case of patients intolerant to steroids or the infusion procedure, mostly driven by their lower cost.

ACTH has been used for decades to treat MS exacerbations. Recent data provides evidence that the beneficial effect of ACTH in other diseases (i.e. nephrotic syndrome, opsoclonus-myoclonus and infantile spasms) may be related not only to its direct induction of corticosteroid production, but also to a corticosteroid-independent melanocortin path.[22]Melanocortins have anti-inflammatory and possible neuroprotective effects and have been shown to improve attention, memory and learning. ACTH binding to central and peripheral melanocortin receptors downregulatesimmunocyte activity, an effect superimposed onto its better known glucocorticoid-mediated actions. In addition, ACTH potentiates

parasympathetic and SNS activity. Both lessen immune responsiveness,[22] and possibly provide neuroprotective effects.

In addition to its effectiveness in treating cognitive relapses and the neuroprotective factors tentatively associated with its administration, ACTH may not only enhance initial recovery, but it may also slow the long-term progression of cognitive impairment. Therefore, we propose to study the influence of Acthar on recovery from cognitive relapses in MS,and to compare this to the influence of corticosteroid administration, as well as to stable MS patients.

2.4 Include complete specific citations/references.

1. Benedict RH, Zivadinov R. Predicting neuropsychological abnormalities in multiple sclerosis. J NeurolSci2006;245:67-72.

2. 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.

3. Foong J, Rozewicz L, Quaghebeur G, Thompson AJ, Miller DH, Ron MA. Neuropsychological deficits in multiple sclerosis after acute relapse. Journal of Neurology, Neurosurgery & Psychiatry 1998;64:529-532.

4. Feuillet L, Reuter F, Audoin B, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. MultScler2007;13:124-127.

5. Glanz BI, Holland CM, Gauthier SA, et al. Cognitive dysfunction in patients with clinically isolated syndromes or newly diagnosed multiple sclerosis. MultScler2007;13:1004-1010.

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

7. Benedict RHB, Zivadinov R. Risk factors for and management of cognitive dysfunction in multiple sclerosis. Nat Rev Neurol2011;7:332-342.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

8. Patti F, Pozzilli C, Montanari E, et al. Effects of education level and employment status on HRQoL in early relapsing-remitting multiple sclerosis. MultScler2007;13:783-791.

9. 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;7:340-344.

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

11. Morrow SA, Jurgensen S, Forrestal F, Munchauer FE, Benedict RHB. Effects of acute relapses on neuropsychological status in multiple sclerosis patients. Journal of Neurology 2011;258:1603-1608.

12. 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.

13. Benedict RH, Cookfair D, Gavett R, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J IntNeuropsycholSoc2006;12:549-558.

14. Smith A. Symbol digit modalities test: Manual. Los Angeles: Western Psychological Services, 1982.

15. Benedict R. Brief Visuospatial Memory Test - Revised: Professional Manual. Odessa, Florida: Psychological Assessment Resources, 1997.

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

17. Benedict RHB, Bruce J, Dwyer MG, et al. Diffusion-weighted imaging predicts cognitive impairment in multiple sclerosis. Multiple Sclerosis 2007;13:722-730.

18. Benedict RHB, Holtzer R, Motl RW, et al. Upper and Lower Extremity Motor Function and Cognitive Impairment in Multiple Sclerosis. J IntNeuropsycholSoc2011;17:643-653.

19. Filippini G, Brusaferri F, Sibley W, et al. Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Cochrane Database Syst Rev 2000;CD001331.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

20. Shah A, Eggenberger E, Zivadinov R, Stuve O, Frohman EM. Corticosteroids for multiple sclerosis: II. Application for disease-modifying effects. Neurotheraputics2007;4:627-632.

21. Frohman EM, Shah A, Eggenberger E, Metz L, Zivadinov R, Stuve O. Corticosteroids for multiple sclerosis: I. Application for treating MS exacerbations. . Neurotheraputics2007;4:618-626.

22. Arnason B, Berkovich R, Catania A, Lisak R, Zaidi M. Mechanisms of action of adrenocorticotropic hormone and other melanocortins relevant to the clinical management of patients with multiple sclerosis. Multiple Sclerosis Journal 2012.

23. Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. Multiple Sclerosis 1999;5:244-250.

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

25. Gronwall DMA. Paced auditory serial addition task: A measure of recovery from concussion. Perceptual and Motor Skills 1977;44:367-373.

26. Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. Psychological Assessment 1996;8:145-153.

27. Benedict RHB. Brief Visuospatial Memory Test - Revised: Professional Manual. Odessa, Florida: Psychological Assessment Resources, Inc, 1997.

28. Benedict RHB, Munschauer F, Linn R, et al. Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. Multiple Sclerosis 2003;9:95-101.

29. Kurtzke JF. Rating neurologic impairment in Multiple-Sclerosis - An Expanded Disability Status Scale (EDSS). Neurology 1983;33:1444-1452.

30. Gilson BS, Gilson JS, Bergner M, et al. Sickness impact profile - Development of an outcome measure of health-care. Am J Public Health 1975;65:1304-1310.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

3.0 Inclusion and Exclusion Criteria

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

Inclusion Criteria:

(1) Identification by clinical care provider of new acute (defined by clinician as a symptom of recent origin developing with a time span of 48 hours) cognitive relapse or supratentorial GAD enhancing lesions on MRI with confirmation of cognitive decline.

(1a) Confirmation of cognitive decline will be obtained by administering the SDMT as a screening procedure for the study. Participants will qualify if they show a > -3 raw score point change onSDMT (relative to baseline identified to meet criteria #4).

(2) Males/Females between the ages of 18-65 years who are capable of understanding and complying with the protocol, speak and write fluent English, and have at least a 9th grade education.

(3) Have a diagnosis of Relapsing Remitting or early Secondary Progressive MS as per revised McDonald's Criteria.

(4) Valid NP testing in the past 4-5 years

(5) EDSS of ≤ 7.0

(6) Have given written informed consent prior to any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to his/her future medical care.

(7) Are capable of performing the requirements of a NP test battery including at least 20/70 near visual acuity by near vision chart, with correction.

Exclusion Criteria:

(1) Have cognitive deficits caused by concomitant medication usage or other significant neurological/psychological disease e.g. Alzheimer's disease, Parkinson's disease, stroke, transient ischemic attack, Vascular Dementia, Huntington's disease, traumatic brain injury, or chronic CNS infection.

(2) Have evidence of any other medical cause(s) of cognitive impairment.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

(3) Have evidence of current major depression as determined by a positive BDI-FS and clinician interview.

(4) Clear new physical signs or symptoms that are referable to the spinal cord, brainstem, or optic nerve.

(5) Evidence on MRI of new lesions in the brainstem, spinal cord, or optic nerve.

(6) Patients with changes to medications known to influence cognition (narcotics, stimulants, etc.) or to disease modifying therapy within one month of study initiation (or within a timeframe deemed high risk by treating physician) will be excluded.

(7) Presence of current infections as determined by clinician interview.

(8) Currently nursing, intentionally seeking pregnancy, or deemed at-risk for unplanned pregnancy.

(9) Any concomitant medication, or medical condition contraindicated with Acthar.

3.2 Describe how individuals will be screened for eligibility.

All participants will undergo study eligibility screening and consenting by a Clinical Research Project Coordinator. The participants will be provided with a description of the required testing for study participation, and any risks will be described in order for the person to make an informed decision regarding voluntary study participation. This is also an opportunity for the person to ask questions regarding the study and the testing components. All study participants who choose to enroll in the study will be asked to sign and date the consent form in front of the Study Coordinator.

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*

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

- 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 or validated in other languages.

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.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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:

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

- *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, open-label study of Acthar administered as treatment for an acute cognitive relapse. Primary and secondary endpoints will be collected prior to Acthar administration and at 3-month follow-up. Comparison will be made to a stable MS control group.

7.2 Describe the duration anticipated to enroll all study subjects.

Enrollment of all study participants 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 analysis, is expected within 5 years.

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Primary measures will include: Symbol Digit Modalities Test,[14] Brief Visualspatial Memory Test- Revised,[15] Paced Auditory Serial Addition Test,[16]and the Multiple Sclerosis Functional Composite (MSFC).[23]These tests are some of the strongest indicators of clinically relevant cognitive change available in MS.

The Symbol Digit Modalities Test (SDMT) will be used to measure visual processing speed. This test presents a stimulus key of numbers paired with abstract symbols at the top of a page. Participants scan the page below the key which has rows of symbols without the paired numbers. The task is to generate the associated numbers orally as fast as possible. We will employ the Rao oral adaptation [24] of the SDMT as the oral presentation has been deemed most appropriate for use with a potentially motor impaired population.[12]

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

The Paced Auditory Serial Addition Test (PASAT)[25] 3 sec interval version will be used as an indicator of working memory performance. The PASAT is an auditory task in which subjects are exposed to single digit numbers voiced every three seconds. After each number presentation, the subject's task is to respond with the sum of the last two digits presented. As each new number is presented, the subject must recall the previous digit, add them together, and respond before the next number is presented.

The Multiple Sclerosis Functional Composite (MSFC)[23] is a composite measure incorporating aspects of cognition, walking speed and manual dexterity. The 25-foot walk, 9-hole peg test, and PASAT 3-sec (described above) are normalized based on an established normative sample and an overall composite z- score is then determined. This composite is frequently used as a primary outcome in clinical trials as it covers three major domains of function potentially impaired in MS.

The Brief Visuospatial Memory Test Revised (BVMTR)[26, 27] is a measure of episodic memory. This task presents a display of six visual designs presented on an 8.5 x 11 piece of paper for three consecutive learning trials. During each trial the stimulus is presented for 10 seconds, after which the participant is asked to draw the figures as accurately as possible in their correct locations. The six designs receive a score of 0, 1, or 2 based on accuracy and location. After a 20-25 minute delay, participants are again asked to recall and draw the designs.

The North American Adult Reading Test (NAART) is a measure of verbal ability. Patients are asked to read a list of words aloud.

Secondary measures will include: self and informant ratings of cognitive problems using the Multiple Sclerosis Neuropsychological Questionnaire,[28] the Expanded Disability Status Scale,[29] the Multiple Sclerosis Impact Scale, the Beck Depression Inventory – Fast Screen, and subscales from the Sickness Impact Profile[30] (an assessment of health related quality of life and activities of daily living). Incidence of adverse events and concurrent medications will also be recorded as potential covariates.

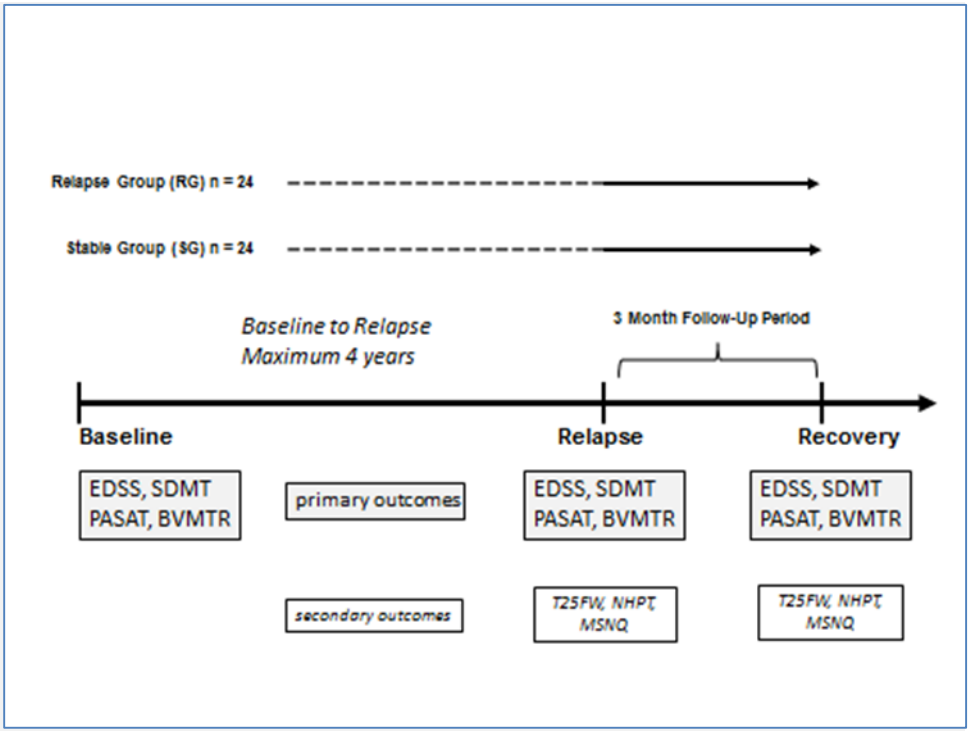
8.2 Describe any primary or secondary safety endpoints.

N/A

9.0 Procedures Involved

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

9.1 Describe and explain the study design.



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.

Initial referral will be initiated by treating physicians. Following confirmation of the subject's relapse status and/or the presence of new supratentorial GAD enhancing lesions, patients deemed eligible for Acthar treatment will be screened for symptoms of infection and evaluated by their treating physician. If the patient agrees, the clinician will contact the research coordinator with the referral.

At this time, all participants will undergo study eligibility screening and consent by a Clinical Research Project Coordinator. The project coordinator or a designated member of the research team will meet, in person, with the participant to discuss the study objectives and procedures, so that he/she can make an informed decision regarding voluntary study participation. Participants will have an opportunity to ask questions regarding the study, procedures, etc. At this time, the study coordinator will administer the SDMT to the relapsing patient. The study coordinator will give this score to another study personnel. At this time the other

study personnel will check the patient's baseline SDMT score. If this score is less than or equal to a 3 point decline, the patient will be deemed eligible for the study. Participants who choose to enroll in the study will then be asked to sign and date a consent form in front of the Study Coordinator.

As described above, enrolled subjects will complete the full cognitive baseline assessment [CVLT2 Learning → BVMTR Learning → SDMT → PASAT → DKEFS Sorting → CVLT2 Delayed Recall → BVMTR Delayed Recall → NAART]. Here the SDMT will be administered a second time to complete the run in for the information processing speed [IPS] composite. Participants will then be guided to complete other patient report questionnaires [BDIFS, FSS MSIS, MSNQ]. Finally, measures of motor function and clinical status will be assessed (EDSS and MSFC).

Acthar Gel will then be administered by a research coordinator to the relapsing patient in accordance with the recommendations set forth in the package insert. The dosage may be individualized according to the medical condition of each patient. Frequency and dose of the drug may be determined by considering the severity of the disease and the initial response of the patient. Acthar will be provided through the study.

As cognitive relapses are typically milder (compared tophysically focused relapses) subjects will be initially dosed for 5 days and pending clinical response or adverse events treatment may be continued for the full 2 weeks in the opinion of the investigator. At study enrollment participants will be instructed on self-administration procedure and supplied with a 5-day course of Acthar® Gel (5ml/80 IU). Medication will be administered through either subcutaneous or intramuscular self-injection (selected by the patient). Patients will be instructed by trained clinical staff on self-administration and will self-administer the first injection under observation in the clinic.

The neuropsychological evaluation takes approximately 45 minutes to complete. The neurological exam takes about 15 minutes. Training and administration of the drug takes about 15 minutes. The neuropsychological assessment will be repeated at 90 days. All participants will be given $200 at the completion of the study. At the time of consenting, each participant will complete a W-9 form. Checks will be mailed from our billing department directly to the participant's address of choice.

The treating neurologist will be responsible for identifying patients agreeing to treatment with the study drug and for insuring that the EDSS is

conducted in a valid manner. Examining technicians will be responsible for administering the neuropsychological testing battery. The Research Coordinator will be responsible for consenting patients, and contacting them on day 7 and day 30 to evaluate for concomitant medications and adverse events. The PI will be responsible for consenting patients, coordinating the database, conducting statistical analysis, coordinating recruitment efforts, and presenting the data.

A detailed clinical assessment will precede enrollment and only patients who agree to be treated with Acthar will be approached for participation.For patients that qualify, Acthar will be provided through the study.

All medications prescribed for patients will be monitored as per PI recommendations. Patients will be evaluated and monitored and all SAEs will be reported to the local IRB within required timelines.

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

A detailed clinical assessment will precede enrollment and only patients who agree to be treated with Acthar will be considered for participation. All serious adverse events will be reported to Mallinckrodt (formerly Questcor) 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.

The Research Coordinator will be responsible for consenting patients, and contacting them on day 7 and day 30 to evaluate for concomitant medications and adverse events. Subjects will also be given the telephone contact information for study staff in case of any late-emerging side effects. Any adverse events will be reported to the PI, the patient's treating neurologist, and the Health Sciences Institutional Review Board at the University at Buffalo Immediately.

Prior to any testing under this protocol, including screening tests and evaluations, all subjects will sign an informed consent form that complies with the requirements of both 21 CFR Part 50 and HIPAA before entering the study. Or, a consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA compliant authorization form for the use of and disclosure of the subject's protected health information (PHI) will be obtained from the subject in accordance with local practice and regulations.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening tests and evaluations.

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

All medications prescribed for patients will be monitored as per PI recommendations. Patients will be evaluated and monitored and all SAEs will be reported to the local IRB within required timelines.

SAEs and unexpected AEs will be collected by the investigator. An SAE is defined as an adverse event that meets any of the following criteria: results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. An unexpected adverse event is an AE either not previously reported or for which the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure. Additionally, the site should report if a patient becomes pregnant during the study and track until an outcome is known. AEs will be documented, evaluated and treated by the investigators according to standard of care (decisions regarding treatment will be made by Investigator Bianca Weinstock-Guttman, MD). All SAEs will be reported to the Institutional Review Board (IRB), as well as RTI-HS (on behalf of Mallinckrodt, formerly Questcor), within 5 business days (unless a different notification schedule is required by the IRB). In the event of a patient death, initial notice will be provided to the IRB and RTI-HS within 24 hours and full details regarding the case will be provided within 5-calendar days. Safety reporting guidelines and relevant forms are supplied in Appendix 1.

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

Acthar Gel will be administered in accordance with the recommendations set forth in the package insert. The dosage may be individualized according to the medical condition of each patient. Frequency and dose of the drug may be determined by considering the severity of the disease and

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

the initial response of the patient. Acthar Gel will be provided to the patient through the study.

As cognitive relapses are typically milder (compared tophysically focused relapses) subjects will be initially dosed for 5 days and pending clinical response or adverse events treatment may be continued for the full 2 weeks in the opinion of the investigator. At study enrollment participants will be instructed on self-administration procedure and supplied with a 5-day course of Acthar® Gel (5ml/80 IU). Medication will be administered through either subcutaneous or intramuscular self-injection (selected by the patient). Patients will be instructed by trained clinical staff on self-administration and will self-administer the first injection under observation in the clinic.

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)
- MS Functional Composite (MSFC)
- Beck Depression Inventory Fast Screen (BDIFS)
- Fatigue Severity Scale (FSS)
- Multiple Sclerosis Impact Scale (MSIS)
- MS Neuropsychological Screening Questionnaire (MSNQ)
- North American Adult Reading Test (NAART)

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

The above-mentioned data will be collected at months 0 and 3.

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.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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.

Neuropsychological testing data and clinical outcome measures will be maintained in de-identified participant charts. These charts will be stored in a locked cabinet and entered into a password-protected database. Appropriate legal guidelines regarding retention of records will be followed. Identifiable data will be destroyed at the earliest possible point. The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. Stored data will be accessed only by the PI and/or designated research staff. The use of stored, de-identified data is undetermined at this time.

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

Neuropsychological testing data and clinical outcome measures will be stored for each participant.

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. Investigator will refer to the Clinical Trial Agreement for details regarding the disclosure of study results.

11.0 Data Management

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

Data will be processed by trained research assistants blind to study hypotheses. Analysis will be conducted using SPSS 22.0. Analysis strategy will be repeated measures analysis of variance where baseline, day 0 and day 90 scores are compared. Analysis of variance will be used

to compare the magnitude of change between day 0 and 90 between the MS patients treated with Acthar and the previously collected controls. Analysis of variance will also be used to compare the magnitude of cognitive recovery after corticosteroid treatment to that after Acthar treatment.

The difference between the means at Day 0 and Day 90 will be used to calculate Cohen's d for each group. To facilitate analysis, all data will be normalized using a large previously published control sample.[13]All tests will be performed based on an alpha of 0.05. Net effect sizes removing estimated practice effects will be calculated using Cohen's d.

11.2 Provide a power analysis.

The selection of 30 as the target enrollment is based on the previously completed study of 25 relapsing and 25 stable MS patients. Five additional patients are planned in order to increase the power of subsequent analyses. A power analysis based on the observed effect of corticosteroids in the relapsing group of d = .56 with 30 participants will be powered >85% to detect effects of a moderate magnitude from Acthar.

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.

All clinical and neurometric assessments will be conducted under the supervision of the PI. All members of research team will complete relevant training programs and courses, including but not limited to: HIPAA, CITI and GRP.

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. Participants will be assigned study identification numbers at enrollment. 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.

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

A Data and Safety Monitor (DSM), comprised of an independent member of the MS-care community without a conflict of interest with the study, will be selected for this study. It will be comprised of a medical professional who is not involved with the conduct of the trial. The DSM will be responsible for evaluating scientific issues related to the study. The DSM will meet with the investigators upon the enrollment of every 10 participants and/or in the event that any adverse, serious or non-serious event occurs, and/or every 6 months or more frequently if deemed necessary. The DSM will be given a detailed progress report before the scheduled meeting. This report will contain safety data summaries: recruitment, visit schedules, missed visits, patient compliance, demographics, outcomes, and adverse events. In addition, copies of all Adverse Events will be included in the report. Also, the DSM will be able to request specific information and analyses to be used for monitoring purposes at any time during the study.

The roles and responsibilities of the DSM will include the following:

- Review protocol, informed consent documents, plans for data safety and monitoring;
- Evaluate study progress, including periodic assessments of data quality and other factors that may affect study outcome;
- Consider external factors such as scientific or therapeutic developments that may impact the safety of the participants or the ethics of the trial;
- Protect the safety and scientific progress of the trial;
- Make recommendations to the Investigators regardingcontinuation, termination, or other modifications to the study based on observed beneficial or adverse events of the treatment under study.

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. Databases will be password protected.

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Each participant will be assigned a study identification number. Data points related to information processing speed, memory, executive functioning, depression, fatigue, and disability will be collected.

11.7 Where and how data or specimens will be stored?

Neuropsychological testing data will be kept in a locked room and in a locked cabinet.

11.8 How long the data or specimens will be stored?

De-identified data will be stored for the remainder of the study and according to appropriate legal guidelines regarding retention of records. De-identified data may be stored indefinitely for future studies, not yet determined.

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.Identifiable data will not be released to any outside sources. Investigator will refer to the Clinical Trial Agreement for details regarding the disclosure of study results.

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

Identifiable data will not be released to any outside sources. Investigator will refer to the Clinical Trial Agreement for details regarding the disclosure of study results.

11.11How data and specimens will be transported?

N/A

12.0 Provisions to Monitor the Data andEnsure 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.

Patients will be assessed for general safety and asked about potential adverse events on day 7 and day 30.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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

Data being reviewed will be patient self-report of general safety and potential adverse events.

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 telephone on day 7 and day 30.

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

Neuropsychological and clinical outcome data will be collected at day 0 and day 90. Information on safety of patient will be collected via telephone on day 7 and day 30.

12.5 Describe who will review the data.

Designated, trained staff under Dr. Ralph Benedict (Primary Investigator) will review neuropsychological, clinical outcome, and safety data. A Data and Safety Monitor (DSM) will also review recruitment, visit schedules, missed visits, patient compliance, demographics, outcomes, and adverse events.

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

Neuropsychological, clinical outcome and safety data will be reviewed at each data collection and additionally by the Data and Safety Monitor (DSM) upon the enrollment of every 10 participants and/or in the event that any adverse, serious or non-serious event occurs, and/or every 6 months or more frequently if deemed necessary.

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

N/A

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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 Actharwas no longer in the patient's best interest, based on treating clinician 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 or if the patient is non-compliant with study procedures.

13.2 Describe any procedures for orderly termination.

In the event of early termination/withdrawal from the study, an in-person exit interview will be conducted by the PI, treating clinician or trained members of the research team.

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 or benefits at the UBMD Neurology. Patients will be free to discontinue participation in the study at any time without fear of penalty or loss of medical care or loss of any benefits to which you may otherwise be entitled. 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.

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.

Risks

There are no risks associated with the neurological examination.

The risks associated with the tests and questionnaires are minimal; there is the possibility that subjects mayexperience some fatigue or frustration. The examiners will do their best to minimize them.

The side effects that may occur with Acthar® are related primarily to its steroid-like effects similar to IV Solumedrol. There may be increased susceptibility to new infection and increased risk of reactivation of latent infections, hence the strict eligibility criteria.

Acthar® may cause various side effects such as:

- Dizziness
- Nausea
- Anaphylactic or hypersensitivity reactions
- Hypertension (high blood pressure)
- Congestive heart failure
- Thin, fragile skin
- Erythema (redness of the skin)
- Increased sweating
- Increased requirements for insulin or oral hypoglycemic (low blood sugar) agents in diabetics
- Elevated blood sugar
- Cushing's syndrome
- Gastrointestinal perforation and bleeding or peptic ulcer
- Pancreatitis (inflammation of the pancreas)
- Abdominal distension (enlargement)
- Water retention
- Peripheral edema (swelling of the extremities)
- Headache
- Impaired wound healing

- Ecchymosis (bruising)
- Menstrual irregularities
- Loss of muscle mass
- Thinning of the bones
- Cataracts
- Glaucoma
- Onset or worsening of euphoria, insomnia, irritability, mood swings, personality changes, depression, anxiety and psychosis
- Fatigue
- Injection site pain

Pregnancy

Women of childbearing potential should not become pregnant during the period of the study. The effect of Acthar® on an unborn baby (fetus) is unknown. If a patient becomes pregnant, continuing the study drug may not be safe for their unborn baby and for themselves. The patient will be advised to report the pregnancy immediately to the site's staff and subject will be removed from the study.

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

There may be other side effects of Actharwhich are unknown at this time.

All patients will be monitoredcarefully for any side effects and will be instructed to report any concerns or changes in their condition to their neurologist. Patients will also be provided 24/7 access to a cellular telephone number used only for research purposes.

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

Women of childbearing potential should not become pregnant during the period of the study. The effect of Acthar® on an unborn baby (fetus) is unknown. If a patient becomes pregnant, continuing the study drug may not be safe for their unborn baby and for themselves. The patient will be advised to report the pregnancy immediately to the site's staff and subject will be removed from the study.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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 is no direct benefit for participating in this study. However, participation may help doctors to learn more about treatments that may help people with MS who have cognitive difficulties.

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

There is no direct benefit to subjects participating in the 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.*

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

- *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 requesting interpretation of neuropsychological tests will be scheduled for a clinical consultation and evaluation by Dr. Ralph Benedict. If a patient reports adverse side effects associated withActhar, the PI and/or research coordinatorwill notify the patient's neurologist.

19.0 Setting

19.1 Describe the sitesor locations whereyour research team will conduct the research.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

All research will be conducted through the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203.

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

All identification of potential subjects will be conducted through the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203, based only on clinical referral. During clinic appointments, relapsing patients will be assessed (by the treating clinician) for suitability for the study. If deemed eligible, and if the patient agrees, the clinician will contact the research coordinator with the referral.

19.3 Identify where research procedures will be performed.

All research procedures will be conducted in private, noise and temperature controlled rooms at UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203.

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 administering neuropsychological tests, interacting with patients, following HIPAA/Good Research practices and guidelines, and obtaining informed consent.The study coordinator is responsible for tracking referrals, recruitment, screening potential subjects, consenting potential subjects, and monitoring patient progress over the course of their enrollment. All research staff has completed CITI and 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 Justifythe 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 in the the UBMD Department of Neurology located on the fourth floor of the Conventus Building at 1001 Main St, Buffalo, NY 14203. Of those, approximately 5-10 patients are seen for urgent visits related to a relapse or an exacerbation. All patients seen by the treating neurologist in this context are considered for this study. All patients referred to the research team are screened.

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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

20.4 Describe your facilities.

Our research is conducted at 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, noise and temperature controlled 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.

Treatment for relapses or other conditions will be used at the discretion of the treating clinician as deemed necessary for the management of the subject. Participants requesting interpretation of neuropsychological tests will be scheduled for a clinical consultation and evaluation by Dr. Ralph Benedict. If a patient reports adverse side effects of Acthar, the PI and/or research personnel will notify the patient's neurologist.

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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 deemed eligible for the study 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.

22.2 Describe the source of subjects.

Subjects will be patients from the UBMD Department of Neurology/JacobsMS Center in Buffalo, NY.

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

No advertisements will be used to identify potential subjects; clinician referrals will be the only means of identifying potential subjects.

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.)

No advertisements will be used for recruitment of subjects.

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

Subjects will be given $200 at completion of the study. At the time of consenting, each participant will complete a W-9 form. Checks and gift cards will be mailed from our billing department directly to the participant's address of choice.

23.0 Local Number of Subjects

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

We will enroll 30 relapsing-remitting MS patients and 30 stable MS patients.

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.)

During routine clinic appointments, cognitively relapsing patients will be assessed (by the treating clinician) for suitability for the study. Subjects who agree to participate and pass screening requirements will be enrolled in the study. Thirty relapsing MS patients and 30 stable MS 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?

Neuropsychological testing data and clinical outcome measures will be maintained in de-identified participant charts. These charts will be stored in a locked cabinet and entered into a password-protected database. Appropriate legal guidelines regarding retention of records will be followed. Identifiable data will be destroyed at the earliest possible point. The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential. Stored data will be accessed only by the PI and/or designated research staff. The use of stored, de-identified data is undetermined at this time.

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

Data will be stored for the duration of the study and according to federal regulations.

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

PI and research staff.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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.

Participants will meet in private interview rooms for in-person participation. When they participate via mail or telephone they are able to determine the privacy of the settings in which they participate.

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. All study procedures, screening, and consenting will be conducted in a private, temperature and noise-controlled room.

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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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

The University at Buffalo has no program to pay for medical care for research-related injury.

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

N/A

27.0 Economic Burden toSubjects

27.1 Describe any costs that subjects may be responsible forbecause 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, temperature and noise controlled testing room.

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

Patient is informed of study procedures when referred to research staff by their neurologist. Consent is obtained prior to any procedures. Participants will be provided adequate time and the opportunity to ask questions.

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 asked to give online consent.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Participant understanding of the procedures, etc. of the study will be confirmed during an in-person interface.

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.

See Section 3.3

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.

See Section 3.3

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:

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

Informed consent will be obtained. This research does not involve deception.

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:

This research does not involve a waiver of consent.

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 NYstate, 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*

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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

28.13 Describe 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

28.14 Indicate 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

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

N/A

Cognitively Impaired Adults

28.16 Describe 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.

Individuals are deemed capable of providing consent when they express an understanding of the study objectives, procedures, etc. Participants will be assessed first by the clinicians during routine clinic visits and then by the research coordinator/designated research staff. Understanding of the study procedures, objectives, etc. will be determined if the participant is able to coherently relay relevant information when asked by the clinician or researcher.

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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.

Inclusion criteria state that patients must be willing and able to provide informed consent. Individuals are deemed capable of providing consent when they express an understanding of the study objectives, procedures, etc. Participants will be assessed first by the clinicians during routine clinic visits and then by the research coordinator/designated research staff. Understanding of the study procedures, objectives, etc. will be determined if the participant is able to coherently relay relevant information when asked by the clinician or researcher.If a participant is cognitively impaired to a degree that he/she does not meet the criteria stated above, he/she will not be eligible for the study. LARs will not be used.

28.18For research conducted outside of NYstate, 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 thisresearch. 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.*

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

- *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

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

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.

Acthar will be provided to the investigators by Questcor and to the patients by the investigators. All drug shipments received will be counted and recorded in a drug accountability binder maintained by the study coordinator. Copies of the receipt of the study drugs as shipped will be kept in the binder. Study drug will be stored in accordance with guidelines provided by Mallinckrodt (formerly Questcor). Study medication will be supplied to patients by trained clinical staff under the supervision of the investigators and self-administration instructions provided verbally and in-writing. Patients will receive sufficient supply of Acthar as prescribed by the investigator (Bianca Weinstock-Guttman, MD), in accordance with the treatment protocol and clinical judgment. Drugs destroyed or accidentally discarded will be accounted for. Unused portions of Acthar will be returned to the investigators following the treatment period and disposed of in accordance with guidelines provided by Mallinckrodt (formerly Questcor).

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:

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.

	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:N/A

PROTOCOL TITLE: Effects of adrenocorticotropic hormone (Acthar gel®) on recovery from cognitive relapses in MS.