Study Title: A Placebo-controlled Double Blind Crossover Trial of Acetylsalicylic Acid as a Pre-treatment for Exercise in Multiple Sclerosis

Unique Protocol ID: AAAQ1758

Document: Study Protocol

Date of Document: 1/30/2017

Columbia University Human Subjects Protocol Data Sheet

General Information

Protocol:	AAAQ1758(M01Y02)	**Protocol Status:**	Approved
Effective Date:	01/30/2017	**Expiration Date:**	12/20/2017
Originating Department Code:		NEU Columbia Neurology (752530X)	
Principal Investigator:		Leavitt, Victoria (vl2337)	
From what Columbia campus does this research originate:		Medical Center	
Title:	Aspirin in Multiple Sclerosis		
Protocol Version #:	1.0	**Abbreviated Title:**	Aspirin in Multiple Sclerosis
Was this protocol previously assigned a number by an IRB:		No	

Is the purpose of this submission to obtain a "Not Human Subjects Research" determination?
No

IRB Expedited Determination

10. Minor change in previously approved research during the period (of one year or less) for which approval is authorized.

Modification Information

Enrollment status:
Open to enrollment or ongoing review of records/specimens
Provide any additional information necessary to explain the study status:
Modification Summary: Provide a description of, and explanation for, all changes being proposed in this submission:
One minor modification to procedures has been made: instead of monitoring biometrics at 60-second intervals throughout the exercise test, we will monitor at 3 minute intervals. We also added the Department of Rehabilitation and Regenerative Medicine as an additional location for this study, as it is where the exercise tests for the exercise subsample will take place.
Does this submission include a report of a protocol violation?
No
If a Protocol Violation is unanticipated, at least possibly related to the research, and involves risks to subjects or others, it should be reported to the IRB within one week (5 business days) as an Unanticipated Problem (UP) in Rascal. For more information please review the IRB Policy on Deviations and Violations: http://www.cumc.columbia.edu/dept/irb/policies/documents/ProtocolDeviationandViolationOct292013finalclean.pdf
Indicate which sections of the Rascal submission are affected by the proposed modification. Each marked section must be revised as part of this submission:

[ ]General Information	[ ]Exempt and Expedited
[ ]Attributes	[ ]Personnel
[ ]Funding	[ ]Background
[ ]Research Aims and Abstracts	[x]Procedures

[ ]Locations
[ ]Data Security and Privacy
[ ]Informed Consent/Recruitment
[ ]No revisions to submission content required
[ ]Subjects
[ ]Risks/Benefits/Monitoring
[ ]Attachments (including Rascal-generated attachments)

Has the consent form been revised in this submission?

No

Does this modification include only administrative changes?

No

Attributes

Special review type: Check all that apply or check "None of the Above" box.

[ ]Review for 45 CFR 46.118 Determination (involvement of human subjects is anticipated but is not yet defined)
[ ]Funding review for Administrative IRB approval (such as for Center or Training Grants)
[x]None of the above

IRB of record information: Will a Columbia IRB be the IRB that is responsible for providing review, approval, and oversight for this study?

Yes

Select the most appropriate response:

Columbia will be the IRB of record for the study procedures conducted by Columbia researchers (Note: this response will apply to most submissions).

Is this research part of a multicenter study?

No

Please indicate if any of the following University resources are utilized:

[ ] Cancer Center Clinical Protocol Data Management Compliance Core (CPDM)
[ ] CTSA-Irving Institute Clinical Research Resource (CRR)
[ ] CTSA- Irving Institute Columbia Community Partnership for Health (CCPH)
[x] None of the above

Background

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives.

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Study Purpose and Rationale:

Provide pertinent background description with references that are related to the need to conduct this study. If this is a clinical trial, the background should include both preclinical and clinical data. Be brief and to the point.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Fatigue is among the most prevalent, debilitating, and refractory symptoms of multiple sclerosis (MS),[1–3] a chronic autoimmune inflammatory disease affecting approximately 400,000 Americans that is typically diagnosed during young or middle adulthood. As one of my MS patients described fatigue: *"It's like having a wet blanket over my shoulders all day long."* For persons with MS, fatigue limits functional independence and encumbers successful achievement of normative goals such as gainful employment and raising a family.[4] Despite much empirical and clinical attention, the underlying mechanism(s) of fatigue are poorly understood. Investigations seeking a neuroanatomical basis for MS fatigue using MRI have produced equivocal results,[5–14] with some studies finding no links,[5–8] and others linking MS fatigue to such varied parameters as lesion load,[12,13] corpus colossal atrophy,[9] parietal atrophy,[6,10,12] frontal atrophy,[10,12] deep gray atrophy,[10,14] and generalized cerebral atrophy.[11,13] These inconsistent, non-specific findings perpetuate uncertainty about the etiology of MS fatigue as well as highlight the likelihood that multiple etiologies underlie MS fatigue. This notion is supported by the heterogeneity of patients' own descriptions of fatigue: some report stable fatigue, while others note day-to-day fluctuations. We currently lack effective treatments for fatigue. Although many patients are prescribed stimulant medication (e.g., modafinil) (likely based on the assumption that fatigue is linked to arousal dysfunction), several randomized clinical trials have failed to support their efficacy to reduce fatigue in MS.[15–18] In contrast, cooling treatments (e.g., cooling garments[19,20], antipyretics[21,22]) have shown promise for reducing MS fatigue. These treatments have yet to be widely embraced, perhaps because underlying mechanisms to support this approach have not been elucidated. **We recently published the first-ever report of elevated body temperature in relapsing-remitting MS (RRMS) patients relative to healthy controls, and elevated temperature was linked to worse fatigue.**[23] Importantly, we have also replicated our original finding in a separate sample collected in Milan,Italy.[24] Our observation of higher body temperature in MS is completely novel, although it may not seem that way. Mention of temperature and the first thing called to mind is 'Uhthoff's phenomenon': Wilhelm Uhthoff's observation in 1890 that MS patients show worse symptoms after heat exposure.[25] This observation motivated a comprehensive body of research to experimentally manipulate/raise body temperature in MS patients to observe worse clinical symptoms.[26–37] Despite all this work, what has been surprisingly missing from the literature until now was an investigation of core body temperature *in the absence of experimental manipulation*. **Our finding that body temperature is elevated and linked to fatigue in RRMS lays the groundwork for a paradigm shift in our understanding and treatment of fatigue.** That is, we shift our focus from exogenous to endogenous temperature, and from stimulant medication to cooling treatments. The current pilot project will interrogate our temperature hypothesis of fatigue in the following ways: 1) establish a link between elevated brain temperature and fatigue, 2) test aspirin as a novel cooling treatment for fatigue in MS targeting elevated body/brain temperature, and 3) explore the impact of reduced brain temperature on efficiency of neural network function using fMRI resting-state functional connectivity analysis.Elevated brain temperature was recently reported in MS patients compared to healthy controls,[38,39] although no study has ever investigated its association to fatigue or its impact on neural network efficiency in MS, or in any clinical

population. Brain temperature can be easily and non-invasively measured using a simple sequence on MRI, magnetic resonance spectroscopy (MRS).[40,41] MRS is easily acquired with MRI and can be used to derive brain temperature with accuracy of ±0.1°C.[40] Additional advantages of MRS thermometry are that it can be acquired within the context of a standard clinical scan, and it does not require the use of contrast. Brain temperature provides valuable prognostic information for a growing number of clinical populations (e.g., acute ischemic stroke,[42–44] neonates with hypoxic-ischemic encephalopathy[45]), although MRS thermometry has been employed in only one MS study to date (revealing elevated brain temperature[38]). As a feasibility study, we used MRS thermometry to measure brain temperature in 14 MS patients and found a link between brain temperature and fatigue .

Exercise has many benefits for persons with multiple sclerosis (MS), and decreased participation in exercise may put MS patients at risk for disability secondary to a sedentary lifestyle. Therefore, encouraging MS patients to exercise is a key priority for clinicians. The challenge to widespread endorsement of exercise is that many MS patients experience exercise-induced short-term discomforts of overheating and exhaustion. In healthy people, exercise causes an increase in core body temperature, which in turn leads to reduced performance. A recent study comparing healthy adults to adults with MS showed that whereas exercise increased body temperature in both groups, only in the MS group was it correlated with exhaustion. The reason for this may relate to our first-ever observation that resting body temperature is elevated in relapsing-remitting MS (RRMS) patients relative to healthy controls. That is, even before being exposed to heat or exercising, people with RRMS are already warmer (note that this is distinct from Uhthoff's phenomenon, which exclusively relates to exogenous heat exposure rather than endogenous core body temperature). Our finding is clinically meaningful, as elevated body temperature was correlated with worse fatigue in our patients. This link provides novel context for several prior successful trials of cooling treatments (e.g., cooling garments, aspirin) for reducing fatigue in MS patients outside of exercising. Likewise, novel but cumbersome cooling treatments (e.g., cooling chambers) administered during exercise in MS have improved exercise performance. This pilot project is the first study of aspirin (acetylsalicylic acid, ASA) as a cost-effective, readily-available, and easily-administered pretreatment before exercise in RRMS to reduce overheating and exhaustion. Exercise Aim: To determine whether pretreatment with ASA (compared to placebo: withinsubject crossover design) before exercise results in improved exercise performance (i.e., increased time-to-exhaustion). We hypothesize that participants will tolerate exercise for longer after taking ASA than placebo. This hypothesis is based on a) demonstrated efficacy of antipyretic for reducing body temperature during exercise in healthy controls, b) demonstrated efficacy of antipyretic for reducing fatigue in non-exercising MS patients, and c) demonstrated efficacy of elaborate (unblinded) cooling treatments (e.g., cooling garments, cooling hand chamber) for improving exercise performance in MS patients. Note that this project is especially important for MS patients, who have a disease-specific body temperature elevation and sensitivity to heat (i.e., Uhthoff's).

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Pountney, E. Effect of raising body temperature on visual and somatosensory evoked potentials in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry* **42,** 250–255 (1979).34. Kazis, A., Vlaikidis, N., Xafenias, D., Papanastasiou, J. & Pappa, P. Fever and evoked potentials in multiple sclerosis. *J Neurol* **227,** 1–10 (1982).35. Zweifach, P. H. Studies of hyperthermia in optic neuropathy. Consideration of a humoral factor. *Arch Ophthalmol* **96,** 1831–1834 (1978).36. Fraser, C. L., Davagnanam, I., Radon, M. & Plant, G. T. The time course and phenotype of Uhthoff phenomenon following optic neuritis. *Mult Scler* **18,** 1042–1044 (2012).37. Romberg, A., Ikonen, A., Ruutiainen, J., Virtanen, A. & Hamalainen, P. The effects of heat stress on physical functioning in persons with multiple sclerosis. *J Neurol Sci* **319,** 42–46 (2012).38. Pietroboni, A. *et al.* Brain temperature in multiple sclerosis. *Mult Scler* (2013). doi:10.1177/1352458513508839. Hasan, K. M., Lincoln, J. A., Nelson, F. M., Wolinsky, J. S. & Narayana, P. A. Lateral ventricular cerebrospinal fluid diffusivity as a potential neuroimaging marker of brain temperature in multiple sclerosis: a hypothesis and implications. *Magn. Reson. Imaging* **33,** 262–9 (2015).40. Zhu, M., Bashir, A., Ackerman, J. J. & Yablonskiy, D. A. Improved calibration technique for in vivo proton MRS thermometry for brain temperature measurement. *Magn Reson Med* **60,** 536–541 (2008).41. Naressi, A., Couturier, C., Castang, I., de Beer, R. & Graveron-Demilly, D. Java-based graphical user interface for MRUI, a software package for quantitation of in vivo/medical magnetic resonance spectroscopy signals. *Comput Biol Med* **31,** 269–286 (2001).42. Marshall, I. *et al.* Measurement of regional brain temperature using proton spectroscopic imaging: validation and application to acute ischemic stroke. *Magn Reson Imaging* **24,** 699–706 (2006).43. Karaszewski, B. *et al.* Early brain temperature elevation and anaerobic metabolism in human acute ischaemic stroke. *Brain* **132,** 955–964 (2009).44. Karaszewski, B. *et al.* Measurement of brain temperature with magnetic resonance spectroscopy in acute ischemic stroke. *Ann Neurol* **60,** 438–446 (2006).45. Wu, T. W. *et al.* Brain Temperature in Neonates with Hypoxic-Ischemic Encephalopathy during Therapeutic Hypothermia. *J Pediatr* (2014). doi:10.1016/j.jpeds.2014.07.02246. Krupp, L. B., LaRocca, N. G., Muir-Nash, J. & Steinberg, A. D. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* **46,** 1121–1123 (1989).47. Téllez, N. *et al.* Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Mult. Scler.* **11,** 198–202 (2005).48. Wingerchuk Keegan, M., Shuster, E., Carter, J., Hentz, J., Thaera, G., Cortez, M., Rodriguez, M., D. Aspirin is unlikely to have a clinically meaningful effect on multiple sclerosis-related fatigue: Data from a randomized controlled trial (P7.245). *Neurology* **82,** Supplement P7.245 (2014).49. Aspirin Comprehensive Prescribing Information. at <www.fda.gov/ohrms/docets/ac/03/briefing/4012B1_03_App 1-Professional Labeling.pdf>50. Cruz Gomez, A. J., Ventura Campos, N., Belenguer, A., Avila, C. & Forn, C. Regional brain atrophy and functional connectivity changes related to fatigue in multiple sclerosis. *PLoS One* **8,** e77914 (2013).51. Finke, C. *et al.* Altered basal ganglia functional connectivity in multiple sclerosis patients with fatigue. *Mult. Scler.* (2014). doi:10.1177/1352458514555788452. Di Martino, A. *et al.* Functional connectivity of human striatum: a resting state FMRI study. *Cereb. Cortex* **18,** 2735–47 (2008).53. Di Martino, A. *et al.* Relationship between cingulo-insular functional connectivity and autistic traits in neurotypical adults. *Am. J. Psychiatry* **166,** 891–9 (2009).54. Tomasi, D. & Volkow, N. D. Association between functional connectivity hubs and brain networks. *Cereb Cortex* **21,** 2003–2013 (2011).55. Thorpe, J. W. *et al.* Serial gadolinium-enhanced MRI of the brain and spinal cord in early relapsing-remitting multiple sclerosis. *Neurology* **46,** 373–378 (1996).56. Barkhof, F. *et al.* Relapsing-remitting multiple sclerosis: sequential enhanced MR imaging vs clinical findings in determining disease activity. *AJR Am J Roentgenol* **159,** 1041–1047 (1992).

Describe the methodology that will be used in this study, covering such factors as retrospective vs. prospective data collection, interventional vs. non-interventional, randomized vs. non-randomized, observational, experimental, ethnography, etc.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

All MS participants will undergo the following procedures:I. Participants will be asked to refrain from eating for 2 hours prior to their arrival at our center. Once here, after the consenting process is finished, participants will have their temperature taken aurally (two measurements will be taken for reliability) and will then complete a simple motor task, the hand dynanometer test (5 measurements will be taken), an objective measure of physical fatigue that has been used in MS (Greim et al, 2007). They will then have their aural temperature measured again, before filling out questionnaires on fatigue (FSS, VAS), mood (BDI-II), and a diary page. Aural temperature will be recorded once again, just before the pill is administered (placebo or aspirin). II. Scan condition:Participants are then scanned for one hour. Immediately after scanning, aural temperature is recorded, followed by the same set of questionnaires, plus one additional questionnaire, the Global Fatigue Change (GFC). All participants will also be asked which pill they think they received, aspirin or placebo. The hand dynanometer test will be completed once again, followed by a final aural temperature measurement. All of these procedures are expected to take under 2 hours.III. Patients who are not scanned will wait quietly for one hour, and then baseline procedures will be repeated [temperature taken aurally (two measurements will be taken for reliability), repeat the hand dynanometer test, complete questionnaires on fatigue (FSS, VAS)].Exercise condition: Ten RRMS patients will be randomized in a crossover double-blind study. After undergoing same procedures as above (section I), each subject in the exercise condition will undergo the following additional procedures: subject will have peak ventilatory capacity (Maximum Voluntary Ventilation, MVV) determined before the exercise test via a Vmax Encore System (CareFusion Corp, San Diego, CA) . Each subject will have a 5-minute resting phase followed by a three-minute warm up and then a progressive ramped exercise test using a VIAsprint 150P lower body cycle ergometer (CareFusion Corp, San Diego, CA) until achieving one of the following VO2max criteria: respiratory exchange ratio (RER) 1.1, increases in ventilation without concomitant increases in VO_2 , maximum agepredicted heart rate and/or volitional fatigue. An individualized ramping protocol will be used as determined by weight and subject's exercise profile as determined by a certified exercise physiologist. Blood pressure, tympanic temperature, and RPEbr and RPElegs data will be collected at 3-minute intervals. Minute ventilation, expired oxygen (O_2), carbon dioxide (CO_2), watts, RER, and total time will be measured using Vmax Encore Metabolic system (Sensormedics, Inc, Loma Linda, CA). Flow sensor and gas analyzer will be calibrated against known medical grade gases before each test. VO2max will be determined from peak 20-second average of the breath-by-breath measurement of VO_2 . Identical test procedures will be carried out after initiation of placebo or ASA. Anaerobic threshold will be determined for each subject using the V-slope technique. The exercise test will commence one hour after pill was administered. Exercise test: Patients will maintain a cycle cadence between 50-60 revolutions per minute (RPM) on the lower body cycle ergometer for the duration of the test. The test will be terminated when the cadence drops below 40 RPM for 5 seconds, or when participant reaches volitional exhaustion [i.e., in the presence of American Thoracic Society (ATS) standard test termination criteria]. In healthy adults, the estimated time to bring about volitional exhaustion is 8-12 minutes. At termination, RPEbr, RPEleg, blood pressure (BP), and tympanic

temperature (right ear) will be recorded (BODY TEMP 2). In addition, participants will record their current level of fatigue with VAS of fatigue and Global Fatigue Change (GFC). Each exercise session will be performed at the same time of day (±1 hour), and between the hours of 11 am and 5 pm. The temperature of the room will be held constant to within ±5 degrees Fahrenheit, and recorded at the start of each session. After each phase (placebo and ASA), participants will be asked which condition they think they were in, to ensure effectiveness of blinding. A sample of 12 healthy controls will be enrolled to obtain normative brain temperature. The HC group procedures will be as follows: After being consented, participants will fill out a BDI-II, FSS, VAS, and a diary page. They will have aural temperature measured before being scanned. After the scan, aural temperature will be measured once again, before participants are asked to fill out questionnaires once again: FSS, VAS, GFC. These procedures are expected to take approximately one hour total.

Statistical Procedures:

Provide sufficient details so that the adequacy of the statistical procedures can be evaluated including power calculations to justify the number of participants to be enrolled into the study. Definitions of subject terms such as enrolled and accrued as used for Rascal submissions can be found in the Subjects section.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Methods and Statistical approach: Scan condition: All participants will be scanned at New York State Psychiatric Institute at CUMC in consultation with Dr. Alayar Kangarlu (Co-I, Senior Physicist and Director of physics and engineering), who assisted in MRS analysis of the feasibility data presented here. Aim 1. We will examine the association of brain temperature in centrum semiovale (all neuroanatomical sites were selected consistent with 38) and fatigue (FSS total score) using a partial correlation controlling for sex, age, and depression (BDI-II total score, consistent with23). Secondary analyses will be conducted using brain temperature in calcarine sulcus and lesion site, and fatigue measured with the MFIS (total score, subscale scores), and VAS of pain, mood, and fatigue. Aim 2. Our primary analysis will determine whether aspirin administration is effective for reducing brain temperature. A 2x2 mixed ANOVA will be run with factors of group (placebo vs. aspirin) and time (Pre vs. Post). Post-hoc tests of all significant effects will be run. A secondary analysis will investigate the impact of aspirin on fatigue. The same 2x2 mixed ANOVA will be run, with VAS of fatigue as the dependent measure. Aim 3: Functional Connectivity analysis. Data preprocessing will be performed with AFNI and the FMRIB Software Library (e.g.,52,53). A recent fMRI RSFC study identified seven primary brain networks in 979 healthy adults, identifying a central "hub" for each network (component of each network most functionally integrated with the rest of the network).54 Guided by the results of this large-scale study, we will place spherical 6-mm radius seed ROIs within the hub of each network. RSFC will thus be derived for each network (consistent with our methods as described in 57). For the full sample (N=20), regressions will be conducted to examine the association of brain temperature and FC within each network. We expect higher brain temperature to be associated with lower FC, particularly in networks previously seen to be impacted by fatigue (e.g., sensorimotor network).50 For our analysis of the aspirin subgroup, a 2x2 mixed ANOVA will be run with factors of group and time to identify FC changes from Pre to Post, which we expect in the aspirin group relative to the placebo group. We expect that aspirin (versus placebo) will increase network connectivity from pre- to post-scan. Finally, support our hypothesis that such changes are due to changes in brain temperature, we will investigate whether the degree of change in network efficiency is correlated with degree of brain temperature change within the aspirin group using 3D regression within AFNI. Exercise condition. This is a within-subject, 2 (ASA, placebo) by 2 (Time 1, Time 2) cross-over trial in which each subject will serve as his/her own control. Subjects will be randomized to one of two sequences: the

first group will receive ASA at the first exercise session and placebo at the second, while those in group 2 will receive placebo at the first session and ASA at the second. Data analysis will proceed as follows. First, all variables will be inspected for outliers or inconsistent values. Variables that display an extremely right skewed distribution with outliers will be transformed using the log transformation. Any remaining outlier values will be dealt with using winsorization, i.e. the extreme values will be censored down to the nearest non-outlier value. Aim: We hypothesize that participants will demonstrate longer time-to-exhaustion after receiving ASA than after receiving placebo (within-subject crossover design). The measure of interest is the length of time (i.e., time-to-exhaustion) spent exercising at each session. This time has no pre-set upper limit, i.e. patients are free to exercise as long as they wish. This means that the time will not be censored. The effects in a balanced 2x2 crossover trial with treatments A and B with outcome measures YAB and YBA in the two groups, respectively, where A and B are the population means for the direct effects of treatments A and B, respectively, represents a sequence effect, represents a session effect, and A and B represent carryover effects of treatments A and B, respectively. Because ASA has only a short-term effect and the wash-out period is more than adequate, we expect no carryover effects. However, we will still test for carryover effects using the test statistic in Wellek et al. Test for differences between treatment effects: The appropriate test statistic will be an unpaired t statistic on the within-subject differences in outcome between Session 1 and Session 2 (in this order), comparing sequence group AB: YAB1i-YAB2i, and sequence group BA: YBA1j-YBA2j, over all subjects i=1,...,n1 and j=1,...,n2 . Significance level for the difference will be reported using the probabilities from the t distribution with n1 + n2 -2 degrees of freedom. Alternative analysis method: If the observed time measure Y has many outliers and the log transformation is not appropriate, the non-parametric Wilcoxon test will be used in place of the unpaired t-test. Given the pilot nature of this study, we make no power calculations; rather, effect size will be determined from analysis of these preliminary data.

Exempt and Expedited

Is the purpose of this submission to obtain an exemption determination, in accordance with 45CFR46.101(b):
No

Is the purpose of this submission to seek expedited review , as per the federal categories referenced in 45CFR46.110?
No

Funding

Is there any external funding or support that is applied for or awarded, or are you the recipient of a gift, for this project?
Yes

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State /Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
Foundation/Pr	NMSS	[redacted]	[redacted]	[redacted]	[redacted]	Entire	PT-

Award Type	Funding Source Name	Name of awarding agency	Status	Award # or Application Date	Federal/State /Local Government Direct or Subcontract	What is the award covering?	Rascal PT Number
ivate						Protocol	AABL2375

Locations

Location Type	Facility Name	Domestic or International	Geographic Location	Local IRB Ethics Approval	Local Site Approval
Columbia/CUMC	Department of Rehabilitation and Regenerative Medicine				
Columbia/CUMC	Neurological Institute				
Columbia/CUMC	Psychiatric Institute				

Personnel

UNI	Name	Role	Department	Edit/View	Obtaining Informed Consent
vl2337	Leavitt, Victoria	Principal Investigator	SGV Research (758230X)	Edit	Y
ab4447	Blanchard, Adam	Other Engaged Personnel	REH Rehab Medicine Rsch (7534603)	View	N
	Roles and Experience: Exercise physiologist				
cg2814	Guo, Chu-Yueh	Investigator	NEU Education (7524203)	View	N
	Roles and Experience: ACLS-certified physician overseeing exercise test				
csr53	Riley, Claire	Investigator	NEU CN Multiple Sclerosis (7525303)	Edit	N
erg2144	Gelernt, Eva	Coordinator	NEU CN Multiple Sclerosis (7525303)	Edit	Y
	Roles and Experience: Eva Gelernt is the research coordinator who will be primarily responsible for enrolling, consenting, and running participants in the study. She has completed all necessary training requirements.				
gmt2115	Tosto, Gabriella	Coordinator	NEU Columbia Neurology (752530X)	Edit	Y
js1165	Stein, Joel	Investigator	REH Core Administration (753420X)	View	N
	Roles and Experience: Advise and oversee exercise component of study				

Training and COI

The PI must ensure that each individual that is added as personnel has met the training requirements for this study (http://www.cumc.columbia.edu/dept/irb/education/index.html). For help identifying which research compliance trainings you may be required to take, visit the Research Compliance Training Finder.

UNI	Name	COI	HIPAA	HSP (CITI)	Research with Minors (CITI)	FDA-Regulated Research (CITI)	S-I	CRC	Good Clinical Practice (GCP)	Genetic Research Consent
vl2337	Leavitt, Victoria	03/03/2016	08/13/2014	05/28/2015	05/28/2015					
ab4447	Blanchard, Adam	09/26/2016	09/26/2016	09/26/2016	09/26/2016	09/26/2016		09/27/2016	09/30/2016	
cg2814	Guo, Chu-Yueh	09/01/2016	08/10/2015	09/09/2016	09/09/2016	09/09/2016				
csr53	Riley, Claire	12/12/2016	07/14/2008	04/13/2015	04/13/2015	04/13/2015				
erg2144	Gelernt, Eva	12/19/2016	12/13/2016	06/30/2016	06/30/2016			12/13/2016	12/13/2016	
gmt2115	Tosto, Gabriella	04/11/2016	04/30/2014	04/07/2015	04/07/2015	04/30/2014		04/30/2014		
js1165	Stein, Joel	03/02/2016	11/10/2008	01/16/2015	03/11/2009	01/16/2015			01/16/2017	

Departmental Approvers

Electronic Signature: Victoria Leavitt (758230X) - Principal Investigator Date: 01/04/2017

Privacy & Data Security

Indicate the methods by which data/research records will be maintained or stored (select all that apply):

[x]Hardcopy (i.e., paper)

Describe where and how the data will be stored:

Study data including questionnaire scores will be stored securely in a password encrypted excel file on the Babylon file server (certified as per the published CUMC IT Certified Environment List, System ID:566) and coded so that the data may be linked to the participants. Any paper documents will be coded and stored in a locked file cabinet that the principal investigator and research coordinator will have access to. Only the principal investigator and the research coordinator will have access to the identifiable data/code key which will also be kept in a password protected file on the secure Babylon file server. Any endpoint devices used would be encrypted according to CUMC IT policy. MRI data will be de-identified of PHI and then coded and transferred onto CD. MR images from the CD will be processed in a CUMC secure computer. Images will be coded, with the code accessible only by the principal investigator and research coordinator. CDs will be kept in a locked cabinet. This is a single center study so there is no transmission to another site.

[x]Electronic

Where will the data be stored?

Y

[x]On a System

[ ]On an Endpoint

Does this study involve the receipt or collection of Sensitive Data?

Yes

If any Sensitive Data is lost or stolen as part of your research protocol, you must inform both the IRB and the appropriate IT Security Office (CUMC IT Security if at CUMC; CUIT if at any other University campus).

What type of Sensitive Data will be obtained or collected? Select all that apply:

[ ]Personally Identifiable Information (PII), including Social Security Numbers (SSN)

Will Social Security Numbers (SSNs) be collected for any purpose?

[x]Protected Health Information (PHI), including a Limited Data Set (LDS)

If any PHI is lost or stolen, you must inform both the IRB and the Office of HIPAA Compliance.

Indicate plans for secure storage of electronic sensitive data: check all that apply

[ ]Sensitive data will not be stored in electronic format

[x]Sensitive data will be stored on a multi-user system

Provide the System ID number for the certified environment in which the Sensitive Data will be stored

566

[ ]Sensitive data will be stored on an encrypted endpoint

Provide a description of how the confidentiality of study data will be ensured, addressing concerns or protections that specifically relate to the data storage elements identified above (e.g. hard copy, electronic, system, and/or endpoint):

All data acquired in this study will be stored with a coded subject number and without the subject's name. All paper forms will be stored in locked file cabinets. The data obtained in this proposal will be in the form of cognitive performance on specific neuropsychological tests and questionnaires, and digitized indices of brain structure from MRI scans of the brain. Data will be collected specifically for research purposes. In addition, data regarding current medical status and neurological history will be obtained from subjects' physicians. This will be done with a signed release of information from the subject.

Is there or will there be a Certificate of Confidentiality (CoC) for this research?

No

Provide a description of the protections in place to safeguard participants' privacy while information is being collected:

Data will be stored in a coded fashion and the code linking the data to PHI will be protected in a secure file server with additional password protection.

Procedures

Is this project a clinical trial?

No

Is this project associated with, or an extension of, an existing Rascal protocol?

No

Do study procedures involve any of the following?

Analysis of existing data and/or prospective record review

No

Audio and/or video recording of research subjects

No

Behavioral Intervention?

Biological specimens (collection or use of)

Yes

Cancer-related research

No

Drugs or Biologics

Yes

Future use of data and/or specimens

Yes

Genetic research

No

Human embryos or human embryonic stem cells

No

Imaging procedures or radiation

Yes

Medical Devices

No

Surgical procedures that would not otherwise be conducted or are beyond standard of care

No

Will any of the following qualitative research methods be used?

Survey/interview/questionnaire

Yes

NOTE: You must attach a PDF version of the survey(s)/interview(s)/questionnaire(s) to this protocol prior to submission.

Systematic observation of public or group behavior

No

Program evaluation

No

Will any of the following tests or evaluations be used?

Cognitive testing

No

Educational testing

No

Non-invasive physical measurements

Yes

Taste testing

No

Is there an external protocol that describes ALL procedures in this study?

No

Please describe ALL study procedures in detail.

NOTE: Be sure to detail all of the procedures above to which a "yes" response was selected. Also detail any additional procedures that may or may not fall into the categories listed above.

The current pilot project will interrogate our temperature hypothesis of fatigue in the following ways: 1) establish a link between elevated brain temperature and fatigue, 2) test aspirin as a novel cooling treatment for fatigue in MS targeting

elevated body/brain temperature, 3) explore the impact of reduced brain temperature on efficiency of neural network function using fMRI resting-state functional connectivity analysis, and 4) investigate whether pretreatment with aspirin (compared to placebo) before exercise increases performance (i.e., time to exhaustion).

Scan condition: 20 RRMS patients will serve in the scan condition. All participants will be asked to refrain from eating 2 hours prior to their scheduled appointment. Participants will be scanned with MRS to derive brain temperature; fatigue will be measured with validated self-report fatigue questionnaires (FSS 46) and body temperature will be measured with an aural thermometer (Braun ThermoScan IRT 4520 Aural thermometer, consistent with our prior studies23,24) immediately prior to scanning. We hypothesize that higher brain temperature in RRMS patients is correlated with worse fatigue. 10 patients will be randomized to aspirin group (standard dose, 650 mg in 1 pill), and 10 patients to placebo (placebo, 650 mg in 1 pill). After being administered aspirin/placebo, patients will have temperature measured aurally and then receive a scan. We hypothesize that brain temperature will decrease in the aspirin group compared to the placebo group. As a secondary outcome, we will examine change in fatigue after aspirin/placebo administration to see whether the aspirin group experienced a greater decrease in fatigue than placebo group. 12 healthy controls will be enrolled to obtain normative brain temperature. These subjects will fill out questionnaires, have temperature taken aurally, and receive a scan. After scanning, aural temperature will be measured and questionnaires filled out. All subjects will receive only 1 scan and only RRMS subjects will be randomized.

All MRIs will be read by study personnel for research purposes, and will also be read by a trained radiologist to screen for the presence of any IFs (incidental findings). If the radiologist sees an IF on a scan, the research team will contact the study subject immediately.

Exercise condition: 10 RRMS patients will serve in the exercise condition to investigate the effect of aspirin/placebo on exercise performance. Patients will be scheduled to come in for two separate sessions, separated by at least one week. After undergoing all no-scan condition procedures as detailed above, participants will be familiarized with Borg's ratings of perceived exertion (RPE) CR10 scale for breathing (RPEbr) and legs (RPEleg) to be completed during and after the exercise session. Exercise sessions: The Human Performance Laboratory is staffed with ACLS and BCLS (basic and advanced cardiac life support) qualified personnel. Exercise tests will be conducted by a certified exercise physiologist who will be accompanied by a physician to ensure safety. All exercise testing equipment is current and certified for use with human subjects. Cardiopulmonary exercise testing is performed using a Carefusion Encore 29 metabolic system (Viasys Healthcare, San Diego, CA). Echocardiogram (ECG) monitoring is done with a twelve lead system attached to the Encore 29 with cardiosoft software (Viasys, Yorba Linda, CA). Maximum aerobic fitness (VO2max) will be measured by a graded exercise test on an Ergoline 150P electronic-braked cycle ergometer (Carefusion, San Diego, CA). Each subject will have peak ventilatory capacity (Maximum Voluntary Ventilation, MVV) determined before the exercise test via a Vmax Encore System (Carefusion, San Diego, CA). Each subject will have a 5-minute resting phase followed by a three-minute warm up and then a progressive ramped exercise test until achieving one of the following VO2max criteria: respiratory exchange ratio (RER) 1.1, increases in ventilation without concomitant increases in VO2, maximum age-predicted heart rate and/or volitional fatigue. An individualized ramping protocol will be used as determined by weight and subject's exercise profile as determined by a certified exercise physiologist. Blood pressure, tympanic temperature, and RPEbr and RPElegs data will be collected at 3-minute intervals. Minute ventilation, expired oxygen (O2), carbon dioxide (CO2), watts, RER, and total time will be measured using Vmax Encore Metabolic system (Carefusion, San Diego, CA). Flow sensor and gas analyzer will be calibrated against known medical grade gases before each test. VO2max will be determined from peak 20-second average of the breath-by-breath measurement of VO2. Identical test procedures will be carried out after initiation of placebo or ASA (double blind will be maintained). Anaerobic threshold will be determined for each subject using the V-slope technique.

Exercise test: Patients will maintain a cycle cadence between 50-60 revolutions per minute (RPM) for the duration of the test. The test will be terminated when the cadence drops below 40 RPM for 5 seconds, or when participant reaches volitional exhaustion [i.e., in the presence of American Thoracic Society (ATS) standard test termination criteria]. In healthy adults, the estimated time to bring about volitional exhaustion is 8-12 minutes. At termination, RPEbr, RPEleg, blood pressure (BP), and tympanic temperature (right ear) will be recorded. In addition, participants will record their current level of fatigue with VAS of fatigue and Global Fatigue Change. Each exercise session will be

performed at the same time of day (±1 hour), and between the hours of 10 am and 5 pm. The temperature of the room will be held constant to within ±5 degrees Fahrenheit, and recorded at the start of each session.
In addition, we will recruit 30 RRMS patients into a "no-scan" condition in which they will undergo all study procedures except the scan.
All participants will be asked at the end of their session(s) whether they think they received aspirin or a placebo, to ensure effectiveness of blinding.

Biological Specimens

Add an individual entry for each human specimen type that will be collected or utilized for the proposed study. For each specimen type, indicate the source or sources from which you will obtain the specimens.

The use of specimens for research purposes may require that informed consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) be obtained from subjects.

Type:
Urine
Source:
[x] From Columbia and/or NYP Subjects/Patients or Repositories managed by Columbia
Select all that apply to this specimen type:
[x] Specimens will be prospectively collected specifically for this research.
[ ] Residual specimens from clinical care that would otherwise be discarded have been or will be collected.
[ ] Specimens to be analyzed will be (or have been) collected from a commercial source.
[ ] Specimens to be analyzed will be (or have been) collected under a separate CU IRB-approved protocol; this could be an approved research repository protocol.
[ ] From Non-Columbia/NYP Subjects/Patients or Repositories not managed by Columbia
Description of Specimen and Method of Obtaining:
Urine Pregnancy test
Indicate the manner in which the specimens will be labeled:
[ ] Specimens will be labeled with direct identifiers
[x] Specimens will be labeled with a code and the research team has the key and can link specimens to direct identifiers. This code would be considered an indirect identifier
[ ] The identifiers will be removed prior to the receipt of the specimens by Columbia researchers and no link will remain
[ ] Specimens were originally collected without identifiers

If specimens are collected or received at any point in time as with direct or indirect identifiers by the current researchers, then the specimens are considered to be identifiable, and the requirements for Informed Consent (or a waiver, if applicable) and HIPAA Authorization (or a waiver, if applicable) apply. The necessary information will need to be included in the respective sections of this Rascal submission.

Drugs/Biologics

On the General Information page you have indicated that the protocol version associated with the use of this

drug/biologic is as follows: 1.0

Please note that a Protocol Version # is required for protocols using a drug or biologic, and you will not be allowed to submit this protocol until the Protocol Version # field is complete. Please ensure that the Protocol Version # is completely and accurately reported on the General Information page.

List each drug or biologic that will be administered as the object of the protocol or is being used because it is relevant to the aims of the research protocol. This applies whether the drug/biologic is not yet FDA-approved (i.e., is investigational), is FDA approved and used in accordance with its labeling, or is an approved product that is being used in an investigational manner (i.e., off-label use is being studied).

Note that the questions apply only to drugs used in clinical investigations. Emergency use of a drug that is not yet FDA-approved is not a clinical investigation, and a submission in Rascal may not be required. Please contact the IRB for assistance if emergency use of a drug or biologic that is not yet FDA-approved is being considered: (212) 305-5883.

Name:
Aspirin
Dose:
650 mg
Study phase:
Phase 3
Manufacturer Information

Name:	McKesson Brand
Address:	One Post Street San Francisco, CA 94104 415-983-8300
Contact information:	415-983-8300

Route of administration:
Oral
Is the drug/biologic FDA-approved and used in accordance with its labeling?
Yes
An IND/BB-IND is not required. A copy of the package insert must be attached.

Future Use

For what materials do you anticipate future research use? Select all that apply.
[x]Data
[ ]Biological Specimens
For what materials do you anticipate future research use? Select all that apply.
[x]Some or all data and/or specimens, as applicable, will be retained by Columbia researchers for future use.
How are the materials intended to be used for research in the future?
Current PI will retain the materials and there is no intent to create a repository or share with other CU researchers.
Note: Information provided in original consent forms will be will be considered when an addition of future uses is submitted via modification.
What future uses are anticipated?

Data may be examined retrospectively in the future, however any/all future analyses to be conducted will be specific to the research analyses and aims outlined under this protocol.

How will the data and/or specimens, as applicable, be labeled during storage for future uses.

[x]In the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous)

[ ]In a different manner than during collection. Select all that apply:

Describe the physical storage for the specimens/data, including location.

[x]In the same manner as during collection

[ ]In a different manner than during collection

Describe who will have access to the stored data and/or specimens.

The Principal Investigator and study coordinator will have access to the stored data.

[ ]Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

Imaging Procedures/Radiation Therapy

Will a contrast agent (e.g. gadolinium) be used in conjunction with radiation exposure that goes beyond the parameters established for the applicable standard of care (SOC), or will a contrast agent be administered for research purposes only?

No

For each type of radiation exposure (e.g., ionizing: CT, X-ray; non-ionizing: MRI), identify the procedure and whether the administration (e.g., radiation dosage, number or type of scans) is clinically indicated and in accordance with the parameters established for the applicable standard of care (SOC), or is "beyond" these parameters (i.e., includes procedures or exposure for research purposes only).

Procedure(s) Involving Ionizing Radiation

No data to display

Procedure(s) Involving Non-Ionizing Radiation

Procedure	The exposure to:
MRI	As established for the applicable SOC
fMRI	As established for the applicable SOC

Recruitment And Consent

Recruitment:

Describe how participants will be recruited:
Our sample will consist of 20 persons with a clinically definite relapsing-remitting MS (RRMS) in the scan condition, 30 RRMS patients in the no-scan condition, and 10 RRMS patients in the exercise condition. Subjects will be recruited through Dr. Claire Riley, Director of the MS Center at CUMC. Dr. Riley has an active practice with over 1000 MS patients, an estimated 60% of whom meet the subtype (RRMS) criterion for inclusion in this study. Dr. Riley is committed to meeting the recruitment goals of this grant-funded project.
Healthy controls (12 subjects) will be family members of those patients being seen at the MS center. While the study is being explained to the patient by Dr. Riley, family members will also be invited to participate. If they agree, they will be contacted by the study coordinator.

Select all methods by which participants will be recruited:

[ ] Study does not involve recruitment procedures
[x] Person to Person
[ ] Radio
[ ] Newspapers
[ ] Direct Mail
[ ] Website
[ ] Email
[ ] Television
[ ] Telephone
[ ] Flyer/Handout
[ ] Newsletter/Magazine/Journal
[ ] ResearchMatch
[ ] CUMC RecruitMe

Informed Consent Process:

Informed Consent Process, Waiver or Exemption: Select all that apply

[x] Informed consent with written documentation will be obtained from the research participant or appropriate representative.

Documentation of informed consent is applicable to:
The study in its entirety

Identify the portion of the study (e.g., prospective portion, focus groups, substudy 2) or subject population for which documentation of consent will be obtained::

Documentation of participation will be obtained from::

[x] Adult participants
[ ] Parent providing permission for a child's involvement
[ ] Legally Authorized Representatives (LARs)

Describe how participants' written consent will be obtained:
Consent will be obtained by one of the study's research coordinators, Gaby Tosto or Eva Gelernt, or the study PI, Victoria Leavitt, Ph.D., Assistant Professor of Neuropsychology. A consent form requiring signature will be presented in writing and verbally reviewed with each subject in-person at the time of

study enrollment.

Informed consent is not required for exempt research but is recommended for such research when there will be interaction with research participants for the purpose of the research.

[ ] Informed consent will be obtained but a waiver of written documentation of consent (i.e., agreement to participate in the research without a signature on a consent document) is requested.

[ ] A waiver of some or all elements of informed consent (45 CFR 46.116) is requested.

[ ] Planned Emergency Research with an exception from informed consent as per 21 CFR 50.24.

[ ] Informed consent is not required; this is exempt research.

Subject Language

Enrollment of non-English speaking subjects is not expected.

During the course of the study, if non-English speaking subjects are encountered, refer to the IRB's policy on the Enrollment of Non-English Speaking Subjects in Research for further details (http://www.cumc.columbia.edu/dept/irb/policies/documents/Nonenglishspeakingsubjects.Revised.FINALDRAFT.111909.website.doc

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Capacity to Provide Consent:

Do you anticipate using surrogate consent or is research being done in a population where capacity to consent may be questionable?

No

Research Aims & Abstracts

Research Question(s)/Hypothesis(es):

Aim 1 will establish the association of brain temperature and fatigue in a sample of 20 RRMS patients and 12 healthy controls. Participants will be scanned with MRS to derive brain temperature; fatigue will be measured with validated self-report fatigue questionnaires (FSS and MFIS46,47) and body temperature will be measured with an aural thermometer (Braun ThermoScan IRT 4520 Aural thermometer, consistent with our prior studies23,24) immediately prior to scanning. We hypothesize that higher brain temperature in RRMS patients is correlated with worse fatigue.Aim 2 investigates the effect of aspirin administration on brain temperature and fatigue. Two randomized controlled trials (RCTs) of aspirin to reduce fatigue in RRMS were successful,21,22 although a subsequent RCT was discontinued due to small effect sizes.48 None of these studies considered the link between fatigue and body temperature, and therefore did not selectively recruit MS patients with elevated body temperature, as we will for this pilot project. By doing so, we maximize our opportunity to reduce body/brain temperature. Of the twenty RRMS patients, ten patients will be randomized to aspirin group (standard dose, 650 mg in 1 pill), and ten patients to placebo (placebo, 650 mg in 1 pill). Before being administered aspirin/placebo,

participants will rate their fatigue, pain, and mood using a visual analogue scale (VAS) and have their body temperature measured again. After the scan is complete, we will repeat these measures. We hypothesize that brain temperature will decrease in the aspirin group compared to the placebo group. As a secondary outcome, we will examine change in fatigue after aspirin/placebo administration to see whether the aspirin group experienced a greater decrease in fatigue than placebo group.Aim 3 investigates fMRI resting-state functional connectivity before and after aspirin/placebo administration. Given fMRI evidence for disrupted neuronal network connectivity in MS patients with fatigue,50,51 we will explore the impact of aspirin and expected brain temperature changes on neuronal network efficiency. We hypothesize that (a) aspirin (versus placebo) will increase functional connectivity (which has been linked to greater neural efficiency) within networks previously linked to MS fatigue, and (b) degree of temperature reduction within the aspirin group will be correlated with degree of change in neuronal network efficiency. There has never been a study to experimentally manipulate brain temperature and examine the impact on brain function in any clinical population. Aim 4 investigates aspirin (vs placebo) administered before exercise to increase performance (i.e., increase time to exhaustion). The effect of aspirin before exercise on body temperature will also be examined to determine whether increased timeto-exhaustion is correlated with a smaller increase in body temperature after aspirin compared to placebo.

Scientific Abstract:

Fatigue is among the most prevalent, debilitating, and refractory symptoms of multiple sclerosis (MS), a chronic autoimmune inflammatory disease affecting approximately 400,000 Americans that is typically diagnosed during young or middle adulthood. For persons with MS, fatigue limits functional independence and encumbers successful achievement of normative goals such as gainful employment and raising a family. Despite much empirical and clinical attention, the underlying mechanism(s) of fatigue are poorly understood. Investigations seeking a neuroanatomical basis for MS fatigue using MRI have produced equivocal results, with some studies finding no links, and others linking MS fatigue to such varied parameters as lesion load,corpus colossal atrophy,9 parietal atrophy, frontal atrophy, deep gray atrophy, and generalized cerebral atrophy. Inconsistent, non-specific findings perpetuate uncertainty about the etiology of MS fatigue as well as highlight the likelihood of multiple etiologies for MS fatigue. This notion is supported by the heterogeneity of patients' own descriptions of fatigue: some report stable fatigue, while others note day-to-day fluctuations. We currently lack effective treatments for fatigue. Although many patients are prescribed stimulant medication (e.g., modafinil) (likely based on the assumption that fatigue is linked to arousal dysfunction), several randomized clinical trials have failed to support their efficacy to reduce fatigue in MS. For this study, 20 relapsing-remitting multiple sclerosis patients and 12 healthy controls ages 18-65 will be recruited. They will undergo temperature readings, questionnaires, and an fMRI. This data will be used to establish the association of brain temperature and fatigue. We hypothesize higher brain temperature is correlated with worse fatigue.10 patients will be randomized to aspirin group (standard dose, 650 mg in 1 pill), and 10 patients to placebo (placebo, 650 mg in 1 pill). After being administered aspirin/placebo, patients will have temperature measured aurally and then receive a scan. We hypothesize that brain temperature will decrease in the aspirin group compared to the placebo group. As a secondary outcome, we will examine change in fatigue after aspirin/placebo administration to see whether the aspirin group experienced a greater decrease in fatigue than

placebo group. Positive support for our theory may hold dramatic implications for our understanding/treatment of fatigue in MS. Beyond fatigue, adopting MRS thermometry for use in MS represents an opportunity to access a novel and innovative biomarker (brain temperature), which may afford useful prognostic information. The exercise condition of this study examines aspirin as a pretreament to allow MS patients better exercise performance. Exercise provides a multitude of benefits for persons with MS; recent clinical and pre-clinical studies now suggest that exercise has benefits on the neural level (e.g., increased BDNF). Despite this, many persons with MS are deterred from exercising due to the discomfort of overheating and exhaustion that accompany exercise; many know this consequence to be due to Uhthoff's phenomenon. We introduced a critical missing piece to the Uhthoff's story when we provided the first-ever report of elevated resting body temperature in persons with relapsing-remitting MS (RRMS) outside of heat exposure / exercise, and its link to worse fatigue. This project represents the first exercise pretreatment study in MS using acetylsalicylic acid (ASA) to improve exercise performance, and the first exercise study in MS to consider/target elevated resting body temperature as a key factor underlying exercise-related exhaustion. The primary expected benefit of supporting ASA as a pretreatment before exercise to reduce overheating and exhaustion is that it will allow more people with MS to participate in exercise, which in turn will have important implications for improved health, productivity, independence, and quality-of-life in persons with MS. Cumbersome cooling treatments such as cooling garments and vacuum handcooling chambers have been found effective (in unblinded experiments: patients were aware that they were undergoing a cooling manipulation) for improving exercise performance in persons with MS; however their widespread adoption for research and/or clinical use is limited by practicality and lack of standardization. ASA is a simple, cost-effective, readily-available treatment that does not require FDA approval. As the first study of its kind, this project will stimulate future research on ASA exercise pretreatment in MS by our group and others, which will allow for interrogation of the mechanism(s) of ASA, as well as facilitate the development of specific clinical recommendations and treatment protocols.

Lay Abstract:

Fatigue is one of the most common symptoms of MS, experienced by as many as 80% of all patients. One-third of MS patients name fatigue as their most disabling symptom, and fatigue has been linked to loss of employment and reduced quality of life. As one of my MS patients described fatigue: "It's like having a wet blanket over my shoulders all day long." Often, and perhaps most frustrating, sleep is not restorative for people with MS who have fatigue. Fatigue limits functional independence and interferes with successful achievement of goals such as gainful employment and raising a family. Given the severe impact of fatigue on persons with MS, it is surprising that we currently have no effective treatment for it, which may be largely due to our poorly developed understanding of what causes fatigue. The most commonly prescribed treatment for MS fatigue is stimulant medication (like modafinil) although a growing number of clinical trials fail to support benefits of stimulants to reduce fatigue. The use of stimulants is likely motivated by an underlying assumption that fatigue in MS is related to arousal dysfunction, although this link has not been supported. We have shown that elevated body temperature in RRMS patients is linked to worse fatigue. In this project, we measure brain temperature with MRI and examine whether there is also a link to worse fatigue. We will then use aspirin to see if we can a) reduce fatigue, and b) reduce brain temperature.

We will recruit 20 patients with relapsing-remitting MS to serve in this study. First, we will measure their fatigue with self-report questionnaires that are commonly used in MS. Next, we will scan all

participants with MRI. A special sequence called magnetic resonance spectroscopy (MRS) will be used to measure brain temperature. Another sequence (functional MRI, or fMRI) will record brain activity during rest. For the participant, this scan is no different from any other (non-contrast) scans that MS patients are used to getting at an annual visit. Of the 20 participants, ten will be randomized to receive either 1 standard aspirin pill or 1 placebo pill, and they will be blind to their condition. Before and after the scan, subjects will report their levels of fatigue, pain and mood as well as have their body temperature measured.

This pilot study holds immediate and meaningful implications for people with MS, as positive findings would support a novel, inexpensive, and easily obtained treatment for fatigue. Successful completion of this study will pave the way to large-scale research grants to support aspirin as an effective treatment for MS fatigue. In addition, the scientific community will benefit from the adoption of a simple technique to measure brain temperature for use in MS. While MRI has been used to collect brain temperature in other patient populations like stroke patients, it has only been used once in MS. Considering that MS in an inflammatory disease and we now know that relapsing-remitting MS patients have elevated body temperature, looking at brain temperature as an informative marker or predictor of disease activity could be highly useful. This pilot grant could therefore be highly instrumental in bringing to light a straightforward technique for measuring a critical marker of pathology. Researchers will also benefit from our first-ever investigation of how brain temperature impacts brain activity. Despite decades of fMRI work that explores how our brains function, consideration of this simple physiological marker may hold critical implications for our understanding of the brain at work.

Exercise has many benefits for people with multiple sclerosis (MS), such as improved physical symptoms, mood, fatigue, and cognition. However, many people with MS refrain from exercising because of the discomfort of exhaustion and overheating that they experience. The exercise condition of this study investigates the use of aspirin before exercise as a treatment to reduce overheating and exhaustion, thereby availing many more people with MS the opportunity to benefit from exercise.

Risks, Benefits & Monitoring

Abbreviated Submission:

The IRB has an abbreviated submission process for multicenter studies supported by industry or NIH cooperative groups (e.g., ACTG, HVTN, NCI oncology group studies, etc.), and other studies that have a complete stand-alone protocol. The process requires completion of all Rascal fields that provide information regarding local implementation of the study. However, entering study information into all of the relevant Rascal fields is not required, as the Columbia IRBs will rely on the attached stand-alone (e.g., sponsor's) protocol for review of the overall objectives. .

If you select the Abbreviated Submission checkbox and a section is not covered by the attached stand-alone protocol, you will need to go back and provide this information in your submission.

Potential Risks:

Provide information regarding all risks to participants that are directly related to participation in this protocol, including any potential for a breach of confidentiality. Risks associated with any of the items described in the Procedures section of this submission should be outlined here if they are not captured in a stand-alone protocol. Risks of procedures that individuals would be exposed to regardless of whether they choose to participate in this research need not be detailed in this section, unless evaluation of those risks is the focus of this research. When applicable, the likelihood of certain risks should be explained and data on risks that have been encountered in

past studies should be provided.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The risks posed by the methods used in this study are very small. Three trials of aspirin to reduce fatigue in RRMS has been conducted previously, with no adverse events noted. In addition, our study physician, Dr. Claire Riley will work closely during recruitment to ensure that there are no counter indications to one-time aspirin use for any participants. Regarding the MRI/fMRI, the main risk is related to the presence of metal within the body (e.g. non-MRI compatible aneurysm clips, metal shards in the body or eyes, or recently placed surgical hardware) or electronic devices (e.g. pacemaker, cochlear implant). Because the risks of MRI/fMRI to fetuses are believed to be minimal, but are nevertheless not known, females will be given a pregnancy test on the day of the MRI/fMRI scan, and if pregnant will be excluded from the study. In general, participants may experience anxiety or claustrophobia while confined in the small space of the magnet. Participants will be briefed in detail about what they will experience during the scanning session. This should reduce problems related to anxiety or claustrophobia. The scanner is very loud, so participants will be given headphones and earplugs. Participants will be able to be heard by the scanner operator at all times, and will be given a 'panic' button to push at any time in order to be removed from the scanner.

For participants who enroll in the exercise condition, a dedicated study physician (Chu-Yueh Guo) will be available during all exercise sessions and will review all stress tests for any evidence of cardiovascular disease/ischemic changes. In addition, Dr. Claire Riley will ensure that all participants meet inclusion/exclusion criteria (i.e., are physically capable of undergoing exercise testing). The expanded exclusion criteria for the exercise condition include: pulmonary disease, heart disease or other heart problem; vascular disease of the legs, high blood pressure, current medications for high blood pressure or any heart problem; diabetes mellitus or problem with blood sugar levels; lower body weakness or reliance on supportive devices for walking. A certified exercise physiologist (Adam Blanchard) will closely monitor patients throughout all one-on-one sessions, and Dr. Joel Stein will be available for consultation if any concerns arise.

Potential Benefits:

Provide information regarding any anticipated benefits of participating in this research. There should be a rational description of why such benefits are expected based on current knowledge. If there is unlikely to be direct benefit to participants/subjects, describe benefits to society. Please note that elements of participation such as compensation, access to medical care, receiving study results, etc. are not considered benefits of research participation.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Benefits include possible clinical information obtained from the procedures. For example, abnormalities in brain structure or function may be gleaned from analysis of MRI images. With subject's permission, this information will be transferred to the subject's physician. In addition, MS participants in our research studies frequently provide feedback indicating a level of personal satisfaction that they are contributing to science by taking part in research studies.

Alternatives:

If this research involves an intervention that presents greater than minimal risk to participants, describe available alternative interventions and provide data to support their efficacy and/or availability. Note, participants always have the option not to participate in research.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

The alternative to participating in this study is to not participate in this study.

Data and Safety Monitoring:

Describe how data and safety will be monitored locally and, if this is a multi-center study, how data and safety will be monitored across sites as well.

[ ] Abbreviated Submission - This information is included in an attached stand-alone protocol. Proceed to the next question

Data and safety will be monitored to identify unanticipated problems by providing all enrolled subjects with contact information for the study coordinator and the study PI. In addition, over the intervening 3 years between baseline and follow-up, all subjects will be periodically contacted to ensure follow-up participation (i.e., reduce attrition). This contact will also provide study personnel the opportunity to monitor unanticipated problems.

Subjects

Unless otherwise noted, the information entered in this section should reflect the number of subjects enrolled or accrued under the purview of Columbia researchers, whether at Columbia or elsewhere.

Target enrollment:

72

Number enrolled to date:

11

Does this study involve screening/assessment procedures to determine subject eligibility?

No

Is this a multi-center study?

No

Does this study have one or more components that apply to a subset of the overall study population (e.g. Phase 1/2, sub-studies)?

Yes

Name/Procedure	Target enrollment	Enrolled to date	Enrollment Status
Aspirin Experiment	60	10	Open to enrollment or ongoing review of records/specimens
	Addition Information: 20 in the scan condition, 30 in the no-scan condition, 10 in the exercise condition		
Healthy controls	12	1	Open to enrollment or ongoing review of records/specimens

Vulnerable Populations as per 45 CFR 46:

Will children/minors be enrolled

No

Will pregnant women/fetuses/neonates be targeted for enrollment?

No

Will prisoners be targeted for enrollment?

No

Other Vulnerable Populations:

[ ]Individuals lacking capacity to provide consent

[ ]CU/NYPH Employees/Residents/Fellows/Interns/Students

[ ]Economically disadvantaged

[ ]Educationally disadvantaged

[ ]Non-English speaking

[ ]Other Vulnerable populations

[x]None of the Populations listed above will be targeted for Enrollment

Subject Population Justification:

Inclusion/Exclusion criteria: For MS sample, patients must be diagnosed relapsing-remitting MS (RRMS); aged 18-65;exacerbation-free (and no use of corticosteroids) for 6 weeks prior; no prior history of head injury, stroke, other neurological disease/disorder; no current use of antipyretics/pain medication daily; no major depressive disorder / other psychiatric diagnosis; no formally diagnosed sleep disorder. For exercise subsample, additional inclusion criteria: low physical disability [i.e., Expanded Disability Status Scale (EDSS) total score4.5, fully ambulatory without aid]; BMI35 (to reduce health-related confounds of obesity). Additional exclusion criteria: any history of known pulmonary or cardiac disease, and/or cardiac contraindications or contraindications to stress testing as determined by careful chart review/physician consultation.

Does this study involve compensation or reimbursement to subjects?

Yes

Describe and justify reimbursement/compensation:

$25 will be provided for MS participants in the scan and no-scan condition. Participants in the exercise condition will receive $50. Healthy controls will not receive compensation.

Are subjects eligible for compensation of $600 or more in a calendar year?

No

Attached Attestation

Type	Principal Investigator	Date Created
C	Victoria Leavitt	01/04/2017

Attached HIPAA Forms

Number	Type	Title	Status
AAAM8756	A	Aspirin in Multiple Sclerosis	Approve
AAAN5518	D	Pre-screening patients	Approve

Attached Consent Forms

Number	Copied From	Form Type	Title	Active/InActive	Initiator
AAAU9465	AAAU9465	Consent	Aspirin in Multiple Sclerosis	Active	Victoria Leavitt (vl2337)
AAAV1017	AAAV1017	Consent	Aspirin in Multiple Sclerosis_exercise condition	Active	Victoria Leavitt (vl2337)

Documents

Archived	Document Identifier	Document Type	File Name	Active	Stamped	Date Attached	CreatedBy
No	HC_consent form_12 2016 modification	Consent Form/Addendum	HC_consent form_12 2016 modification.pdf	N	Y	12/14/2016	Emily Brooks (eb3092)
No	consent unapproved_april 2016_hc_TRACKED	Consent Form/Addendum (tracked)	consent unapproved_april 2016_hc_TRACKED.pdf	Y		04/04/2016	Gabriella Tosto (gmt2115)
No	consent unapproved_april 2016_rrms_TRACKED	Consent Form/Addendum (tracked)	consent unapproved_april 2016_rrms_TRACKED.pdf	Y		04/04/2016	Gabriella Tosto (gmt2115)
No	consent_approved 2016_TRACKED	Consent Form/Addendum (tracked)	consent_approved 2016_TRACKED.pdf	Y		04/04/2016	Gabriella Tosto (gmt2115)
No	leavitt_NMSS_award letter	Funding/Grant Application/Subcontract	leavitt_NMSS_award letter.pdf	Y		09/29/2015	Gabriella Tosto (gmt2115)
No	drug insert	Investigator Brochure/Package Insert/Device Manual	drug insert.pdf	Y		09/29/2015	Gabriella Tosto (gmt2115)
No	Revised Approval Letter	Local IRB/Ethics/Site Approval	Revised Approval Letter.pdf	Y		01/04/2017	Deirdre Lombardi (dl2971)
No	Diary page	Study Material/Instrument	Diary page.pdf	Y	Y	09/25/2015	Gabriella Tosto (gmt2115)
No	questionnaires	Study Material/Instrument	NMSS pilot surveys.pdf	Y	Y	09/25/2015	Gabriella Tosto (gmt2115)