COLUMBIA | COLUMBIA UNIVERSITY IRVING MEDICAL CENTER

ASPIRIN FOR EXERCISE IN MULTIPLE SCLEROSIS (ASPIRE): A DOUBLE-BLIND RCT OF ASPIRIN OR ACETAMINOPHEN PRETREATMENT TO IMPROVE EXERCISE PERFORMANCE IN MS

Clinical Trial Protocol

Short Title : *ASPIRE*

Protocol Number: *IRBAAAS2529 (M01Y01)*

Protocol Version: *1.0*

Protocol Date: *01 March 2019*

National Clinical Trial (NCT) Identified Number: *NCT03824938*

Principal Investigator: *Victoria M. Leavitt, Ph.D., Assistant Professor, Columbia University*

Supported by: *The National Institute of Neurological Disorders and Stroke/NIH/DHHS*

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INVESTIGATOR AGREEMENT

I have read the foregoing protocol *[V1.0 01/March/2019]* and agree to conduct the study as described herein.

By signing the protocol, the Investigator agrees to keep all information in strict confidence and to request the same from his/her staff and the Institutional Review Board. Study documents will be stored appropriately to ensure their confidentiality. The Investigator should not disclose such information to others without authorization, except to the extent necessary to conduct the study.

_____ 3/01/2019

Investigator Signature **Date**

Victoria M. Leavitt

Print Investigator's Name

SIGNATURE PAGE

Study Number: AAAS2529

Principal Investigator Approval:

Signature:  Date: 03/01/2019

Name: Victoria M. Leavitt

STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.]

OR

(2) [The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.]

LIST OF ACRONYMS, ABBREVIATIONS, AND DEFINITIONS OF TERMS

AE	Adverse Event
APAP	Acetaminophen
ASA	Aspirin
CCC	Clinical Coordination Center
CDE	Common Data Elements
CFR	Code of Federal Regulations
CIRB	Central Institutional Review Board (reference to CUMC IRB)
CRF	Case report form
CS	Clinically Significant
CUMC	Columbia University Medical Center
DCC	Data Coordination Center
DM	Data Management
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IMM	Independent Medical Monitor
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
NINDS	National Institute of Neurological Disorders and Stroke
PPI/PI	Protocol Principal Investigator
PSC	Protocol Steering Committee
PwMS	Persons with Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SOA	Schedule of Activities

SYNOPSIS

Study Title: AAAS2529 (M01Y01): Aspirin for Exercise in Multiple Sclerosis (ASPIRE): A Double-Blind RCT of Aspirin or Acetaminophen Pretreatment to Improve Exercise Performance in MS

Objectives: The overarching objective of this clinical trial is treatment of exercise-induced overheating in persons with RRMS.

Primary Outcome Measure:
Time-to-exhaustion [Time Frame: from start of exercise test until self-reported exhaustion, up to 30 minutes]

- Duration of time exercising before reaching peak exertion, defined as cadence drop below 40 RPM for >/= 5 seconds, or patient reaches volitional exhaustion in accordance with American Thoracic Society standard test termination criteria.

Secondary Outcome Measures:
Exercise-induced body temperature increase [Time Frame: from start of exercise test until self-reported exhaustion, up to 30 minutes]

- Change in body temperature from pre- to post- maximal exercise test

1. Aim 1a. Hypothesis: Compared to placebo, Aspiring (ASA) will result in longer Time to Exhaustion (TTE).
2. Aim 1b. Hypothesis: Compared to placebo, ASA will result in reduced exercise-induced body temperature increase.
3. Aim 2a. Hypothesis: Compared to placebo, Acetaminophen (APAP) will result in longer TTE.
4. Aim 2b. Hypothesis: Compared to placebo, APAP will result in reduced exercise-induced body temperature increase

Design and Outcomes:
This study is a prospective, single-center, blinded, within-subject effectiveness study in patients diagnosed with RRMS. The study will enroll at least 60 patients. The study will entail 3 study visits, separated by no less than 7 days.

The study design consists of:

- Within-subject crossover placebo-controlled experiment with 3 arms. Participants will be randomized to treatment schedule by study biostatistician who will remain double-blind until data collection ceases. Each subject serves as her/his own control.
- This is a Phase 3 study.

The study outcomes are listed as follows:

- Aim 1 uses a two-armed crossover trial to assess differences in outcomes between ASA and placebo; unpaired t-tests will be used to test within-subject differences in outcomes between session 1 and session 2.

- Aim 2 uses a two-armed crossover trial to assess differences in outcomes between APAP and placebo; analytic approach is identical to Aim 1.
- A sub-analysis of Aim 2 uses an ANOVA to assess difference in outcomes among three treatments (ASA, APAP, placebo). All variables will be inspected for outliers or inconsistent values. Variables that display an extremely right skewed distribution with outliers will be transformed using log transformation. Any remaining outlier values will be winsorized, i.e. extreme values will be censored down to the nearest non-outlier value.

Interventions and Duration

- This study will utilize a crossover assignment.
- This study has a 24-month timeline beginning when the study opens enrollment through the completion of data analyses.
- Each subject will be on study for anywhere between 3 and 12 weeks, depending on the scheduling of each exercise session.
- Enrollment is expected to remain open throughout the course of the study until the target goal of 60 completed participants has been reached.
- Interventions in this study include a 650 mg dose of aspirin, acetaminophen, and placebo to be taken orally one hour prior to each exercise session.

Sample Size and Population

- 60 persons randomized
- Persons with current diagnosis of RRMS (2010 McDonald criteria)
    - Pilot trial findings of elevated body temperature in MS were limited to RRMS; Patients with progressive MS may experience exercise-induced exhaustion for different reasons (e.g., increased physical disability); This study limits recruitment to RRMS where pilot findings and a priori hypothesis suggest greatest benefits.
- Persons aged 18 to 65 years
    - Consistent with observations that 75% of relapse-onset MS patients are diagnosed between ages 20 and 50, with a mean onset at 30 years, these limits ensure that our sample is representative of the relapse-onset MS population; Upper limit is set to reduce effects of age-related activity-level decreases.
- Self-reported heat-sensitivity to exercise
- Expanded Disability Status Scale (EDSS) total score ≤ 6.0
    - Patients with higher EDSS scores may experience exercise-induced exhaustion for different reasons (e.g., increased physical disability)
- Exacerbation-free (and no use of corticosteroids) for 6 weeks prior to enrollment
    - To avoid any transitory changes in disability related to current disease activity
- BMI ≤ 35
    - To reduce health-related confounds of obesity.

- When indicating how many subjects will be included in the study, the number of subjects to be ***enrolled*** should be the number of subjects who are expected to be ***consented***. The number of subjects to be ***randomized*** should only include the number of subjects who are expected to receive either the study intervention or placebo (if applicable).

Please note that the Central IRB defines "enrolled" as "consented," and therefore they may issue a ReqMod if the terms "enrolled," "consented," and "randomized" are used interchangeably.

Additionally, if the number of anticipated enrollments is higher than the number of anticipated randomizations due to anticipated screen failures, please state this explicitly.

STUDY OBJECTIVES

1.1 Primary Objectives

Objectives	Corresponding Endpoints
Primary Objective:	
• To evaluate the effectiveness of ASA and APAP (compared to placebo) in reducing exercise-induced overheating in PwMS	• Aural body temperature
• To evaluate the effectiveness of ASA and APAP (compared to placebo) in reducing exercise-induced exhaustion in PwMS	• Self-reported exhaustion • Time to exhaustion • Global Fatigue Change • Fatigue Severity Scale

- Aim 1 uses a two-armed crossover trial to assess differences in outcomes between ASA and placebo; unpaired t-tests will be used to test within-subject differences in outcomes between session 1 and session 2.

- Aim 2 uses a two-armed crossover trial to assess differences in outcomes between APAP and placebo.; analytic approach is identical to Aim 1.

- A sub-analysis of Aim 2 uses a ANOVA to assess differences in outcomes among three treatments (ASA, APAP, placebo).

- All variables will be inspected for outliers or inconsistent values. Variables that display an extremely right skewed distribution with outliers will be transformed using log transformation. Any remaining outlier values will be winsorized, i.e. extreme values will be censored down to the nearest non-outlier value.

- ***The primary objective should always be to address a specific hypothesis.***

- ***State the hypothesis in quantifiable terms: e.g., "the experimental treatment will result in 12 months of additional survival compared to the control treatment."***

- ***For statistical purposes, it may be worthwhile to state both the null and the alternative hypotheses***

- ***This primary objective must match the one used in section 9, Statistical Design***

1.2 Secondary Objectives

Objectives	Corresponding Endpoints
Secondary Objective(s):	
• To evaluate the impact of ASA and APAP (compared to placebo) on mood	• HADS • BDI-II • VAS Mood
• To evaluate the impact of ASA and APAP (compared to placebo) on fatigue	• Global Fatigue Change • Fatigue Severity Scale • VAS Fatigue • Hand dynamometer

2 BACKGROUND

2.1 Rationale

Multiple sclerosis (MS) is a prevalent and chronic neurologic disease that impacts individuals on many levels. Exercise holds a multitude of benefits for persons with MS (PwMS), including improved physical function, reduced fatigue, improved mood, and improved cognition. There is now evidence from pre-clinical models for neural-level benefits of exercise including increased BDNF, and reduced myelin and axonal damage. But exercise only works if people do it, and many PwMS are deterred from exercising by overheating, exhaustion, and symptom worsening: "Uhthoff's phenomenon." Our group extended Uhthoff's observation by providing the first-ever report of elevated resting body temperature and its link to worse fatigue in persons with MS; that is, even before exercise, PwMS are already "heated up." This R21 will support a trial of aspirin as a pretreatment for exercise: our pilot data collected in 12 participants show improved exercise performance and reduced exercise-induced body temperature increase after aspirin. For the proposed study, sixty MS patients will be enrolled in a double-blind RCT with three arms: placebo, aspirin, and acetaminophen (APAP). Design is crossover: each participant will complete three exercise sessions separated by 1-week intervals. At each session, body temperature will be measured before administration of a standard adult dose (one 650-mg capsule) of aspirin, APAP, or placebo. One hour later (time to reach peak serum level) participants will complete a progressive ramped maximal exercise test on a lower body cycle ergometer. Body temperature and biophysical/behavioral variables (VO2max, total watts achieved, blood pressure, anaerobic threshold, ratings of perceived exertion) will be recorded throughout the test at regular intervals. Past research in MS has found cooling treatments

(cooling garments, vacuum hand-cooling chambers) effective for improving exercise performance. However, their widespread adoption for research / clinical use is limited by practicality and lack of standardization. Aspirin is a simple, readily available, cost-effective treatment that does not require FDA approval. If successful, this R21 grant may motivate change in clinical care and adoption of ASA therapy for enhancing exercise performance in PwMS. Positive findings from this study will facilitate future research to test whether ASA use improves exercise adherence, increases everyday physical activity levels, and improves overall QOL for persons with MS.

ASA was selected as the agent for use in the current study because: a) it was safe and effective in our pilot study; b) prior (non-exercise) studies in MS have shown efficacy of aspirin to reduce fatigue, and c) prior work in MS supports its favorable safety profile.[6, 8, 9] In those 3 RCTs, no adverse events were reported, and side effects were minimal (i.e., did not differ appreciably from those reported by the placebo group in each study). Importantly, the daily dosage of ASA in those studies (1300 mg/day, for 6 weeks) was much higher than the dosage we will use here (650 mg/1 time administration). In the long term, adoption of ASA as a pre-treatment for exercise would only require the use of aspirin on an as-needed (PRN) basis, thereby minimizing the potential impact of aspirin's side effects. The safety profile for acetaminophen (APAP) is similarly favorable, and patients with any contraindication to APAP use (e.g., severe active hepatic disease, Hepatitis C Virus) will be excluded from the study.

2.2 Supporting Data

Past research in MS has found cooling treatments (cooling garments, vacuum hand-cooling chambers) effective for improving exercise performance. However, their widespread adoption for research / clinical use is limited by practicality and lack of standardization. Aspirin is a simple, readily available, cost-effective treatment that does not require FDA approval. If successful, this R21 grant may motivate change in clinical care and adoption of ASA therapy for enhancing exercise performance in PwMS. Positive findings from this study will facilitate future research to test whether ASA use improves exercise adherence, increases everyday physical activity levels, and improves overall QOL for persons with MS.

2.3 Risk/Benefit Assessment

Risks:

The risks posed by the methods used in this study are minimal. Three doses of 650mg aspirin in RRMS has been conducted previously, with no adverse events noted. In addition, physicians serving as investigators on this study will work closely during recruitment to ensure that there are no counter indications to one-time aspirin use for any participants. Additionally, a study

physician will be available during all exercise sessions and will review all stress tests for any evidence of cardiovascular disease/ischemic changes.

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most cases of liver injury are associated with the use of acetaminophen doses that exceed the recommended maximum daily limits, and often involve more than one acetaminophen-containing product. The most common adverse reactions in patients treated with acetaminophen been associated with cases of acute liver failure, at times resulting in liver were nausea, vomiting, headache, and insomnia in adult patients and nausea, transplant and death. Most of the cases of liver injury are associated with vomiting, constipation, pruritus, agitation, and atelectasis in pediatric patients.

The minimal risks in the study are related to a) ASA/APAP use (which will be minimized by screening for any counter indications of ASA use, and the dosage is a single-dose administration of the standard adult dose (650mg), and prior ASA trials in MS using this dose twice daily for 6 weeks reported no adverse events and found minimal side effects that did not differ from the placebo condition), and b) discomforts of exercise-induced overheating and exhaustion (which will be minimal, as the exercise test is only about 9 minutes in duration, and we anticipate will be ameliorated in the ASA/APAP conditions). These minimal risks are easily managed, and will be closely monitored; as such, the risk/benefit ratio is very favorable.

A certified exercise physiologist will conduct all exercise tests after subjects have been carefully screened (in consultation with Co-I Dr. Riley, MD, and in consultation with Co-I Dr. Stein, MD) to ensure no counter indications to ASA use or to participating in a supervised exercise session involving stationery cycling. All exercise tests are conducted by an experienced ACLS/BCLS certified exercise physiologist, (Nancy Lee, MS) at Columbia University Medical Center in the presence of a physician. Subjects will be briefed in detail about what they will experience during the exercise sessions.

Benefits:

While participants may not benefit directly, participation in research may benefit the community, specifically the MS community. Participants will receive $100 at the completion of their 3rd exercise session.

This study seeks to test aspirin as an effective pretreatment for exercise to improve exercise performance and minimize discomfort related to exhaustion and overheating that serve as deterrents to exercise for many persons with RRMS. Positive findings from this study will potentially provide an effective, inexpensive, readily available, unobtrusive treatment that will avail more persons with RRMS the benefits of exercise. As such, there are potentially far

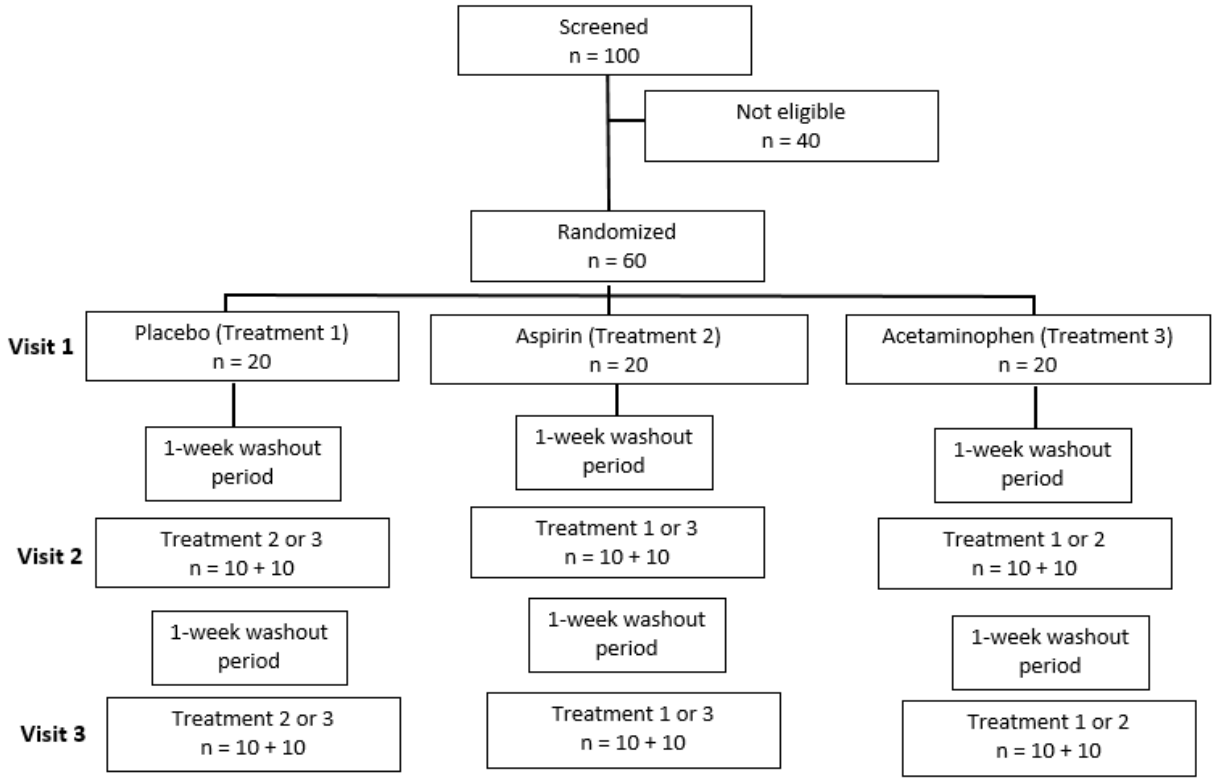
reaching benefits to the MS population associated with the successful completion of this R21 project. A potential immediate benefit for research participants is if they decide that they want to safely incorporate aspirin use into their regular exercise regimen, if they benefit from making that change.

The long-term benefits of exercise for persons with MS are well established. Additionally, new data are now suggesting that sedentary lifestyle is a risk factor for greater disability. Taken together, there is growing motivation to find ways to involve more MS patients in exercise. This study aims to provide a treatment that will reduce the extent of exercise-induced overheating and exhaustion which serve as serious deterrents to exercise for many with MS. The overarching goal of this line of research is to determine whether aspirin use will lead to increased exercise adherence, increased physical activity levels, and improved quality of life. These questions remain to be answered by future research that will only be possible with the initial level of evidence to be provided by this R21 project.

3 STUDY DESIGN

- Design is a within-subject crossover placebo-controlled experiment; subjects will be randomized to one of six sequences (see figure) by study biostatistician who will remain double-blind until data collection ceases. Each participant will attend three exercise sessions scheduled on separate days separated by ≥one-week intervals. Exercise sessions will be scheduled at the same time of day (±1 hour), and between the hours of 10 am-5 pm to reduce the influence of circadian rhythm variability

- Design is crossover: each participant will complete three exercise sessions separated by 1-week intervals. At each session, body temperature will be measured before administration of a standard adult dose (one 650-mg capsule) of aspirin, APAP, or placebo. One hour later (time to reach peak serum level) participants will complete a progressive ramped maximal exercise test on a lower body cycle ergometer. Body temperature and biophysical/behavioral variables (VO2max, total watts achieved, blood pressure, anaerobic threshold, ratings of perceived exertion) will be recorded throughout the test at regular intervals.



3.1 Scientific Rationale for Study Design

Rationale for study design is based on pilot trial upon which the design of this large-scale trial was based (Leavitt et al, 2017).

3.2 Justification for Dose

ASA dose was selected on the basis of prior successful RCTs of ASA to reduce fatigue in non-exercising PwMS.

Whereas past studies gave 650mg twice daily for 6 weeks with no adverse events, this study gives a one-time, single 650mg dose.

3.3 End of Study Definition

The End of Study is defined as follows:

- When 60 participants complete the entirety of the study. A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA).

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

1. Current diagnosis of Relapsing-Remitting Multiple Sclerosis (2010 McDonald criteria)
2. Age 18-65, inclusive
3. Self-reported heat-sensitivity to exercise
4. Expanded Disability Status Scale (EDSS) total score ≤ 6.0
5. Exacerbation-free (and no use of corticosteroids) for 6 weeks prior to enrollment
6. BMI ≤ 40

4.2 Exclusion Criteria

1. Prior history of significant head injury, stroke, or other neurological disease/disorder
2. Current daily use of antipyretics or pain medication
3. Presence of diagnosed major depressive disorder or other diagnosed psychiatric disorders (as determined by medical chart review). Patients with previous or current depression or anxiety not meeting criteria for MDD will not be excluded
4. Diagnosed sleep disorder
5. Vascular disease of the legs, uncontrolled high blood pressure
6. Uncontrolled diabetes mellitus or problem with blood sugar levels
7. Contraindications to aspirin use (history of confirmed peptic ulcer, gastrointestinal or severe gynecological bleeding)
8. Tarry stool or known fecal occult blood
9. Uncontrolled syndrome of asthma, rhinitis, or nasal polyps
10. Daily APAP use
11. Contraindications to acetaminophen use
12. Severe active hepatic disease
13. Hepatitis C Virus
14. Pregnant or breastfeeding

4.3 Lifestyle Considerations

Before testing, participants will be asked to:

- Refrain from eating and drinking (except water) for 3 hours before the exercise test.
- Avoid exercising 24 hours prior to testing day.
- Avoid drinking coffee or caffeine beverages the morning of the test.
- Drink no more than 2 cups of coffee or caffeine beverages the day before the test.
- Consume 4-6 fluid ounces of water 2 hours before testing.
- Avoid supplement consumption other than multivitamins before testing.
- Abstain from casually smoking cigars, cigarettes, and smoky places for at least 3 hours prior to testing.
- Get their normal amount of sleep the night before testing.

- Avoid alcohol consumption prior to testing (No excessive alcohol drinking the night before testing; however, participants who always consume a glass of wine or beer with dinner are allowed to do so).

4.4 Subject Withdrawal Criteria

Subjects may be withdrawn from the study by the PI or Sub-Investigator for one of the following reasons:

- **Adverse event:** clinical event that in the medical judgement of the investigator for the best interest of the patient are grounds for discontinuation
- **Withdrawal of consent:** patient desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the investigator
    - The reason of consent withdrawal will be documented when available.
- Suicidal risk evaluated by suicidal risk assessed by the Hospital Anxiety and Depression Scale (HADS)
- Inability to adhere to the study protocol

4.5 Study Enrollment Procedures

Recruitment:

Sixty patients with RRMS will be recruited from the Multiple Sclerosis Clinical Care and Research Center at the Columbia University Medical Center (CUMC). This center currently sees about forty new MS patients each month, adding to an already large census of MS patients treated at the center annually (approximately 900 patients per year, 60% RRMS). Given the rapid recruitment for the pilot trial [n=12 patients; total pilot duration (recruitment, enrollment, study completion) = 4 months], there is no anticipated difficulty to meet recruitment goals over the 2-year period of this proposed project. We will screen 100 patients, estimating that 60% of screened patients will meet eligibility. Co-I Dr. Riley (Medical Director of the MS Center) and the research coordinator will lead patient recruitment and confirm the disease-specific inclusion criteria.

PPI Dr. Leavitt sees patients at the Center weekly in her role as clinical neuropsychologist, and therefore has an opportunity to identify potential research subjects who will be referred to the study. We do not anticipate any issue with retention, given that the entire duration of study participation is 3 study visits spread over about 3 weeks' time. Enrollment will not be closed until all 60 participants have completed all three visits; this will ensure 60 completed participants are enrolled in this study.

If the patient's treating physician feels the subject may be a good fit for this study based on observations of overheating, fatigue or difficulty with exercising, s/he may discuss the trial with the patient to gauge interest. If the patient is interested in the trial, the treating physician may have a study coordinator or other study personnel meet with the patient to discuss the trial in further detail and answer questions. A screener (attached in Documents) will be reviewed with

the potential participant to ensure criteria are met. If the patient meets criteria and wishes to participate, study personnel will begin the consenting process.

Patients will be referred by the patient's treating physician, many from Drs. Leavitt, Riley and De Jager, who are investigators on this protocol. All other patients will be referred either by colleagues of Dr. Leavitt, all of whom work at the Columbia University Medical Center, or from providers outside CUMC whose patients have seen study flyers and have reached out to a study team member directly to convey interest in the study.

Participants may be recruited via person-to-person methods, as well as via flyers and handouts. All recruitment methods are IRB approved before implementation.

Procedures for Obtaining Informed Consent:

This study utilizes both in-person consenting and e-consent.

E-consent is done via RedCap, a secure online database. A copy of the e-consent form as a Redcap-generated PDF is attached to this protocol to attest to it being identical to the print-version. We will offer the e-consent to in-person participants as a way to replace the signing of a paper-based informed consent as a way to best address the participant's needs or preferences. This is optional and a paper copy will always be available. The e-consent will show the same pages as the traditional paper consent. The potential research participant will then use this e-consent to fill out the same signature fields as the traditional paper consent form. Once the participant signs the consent and hits submit, a PDF of the completed consent will be generated and can be emailed to both the participant and the study coordinator. For both in-person and remote e-consenting, study personnel will abide by the guidelines as highlighted in the Columbia University Institutional Review Board Guidance on Electronic Informed Consent document. For e-consent, study personnel will plan a phone call with each potential participant to discuss the consent form and study in detail, allowing for each participant to ask any questions prior to signing on the online ICF. Study personnel will confirm the participant's identity by asking for the patient's full name and DOB prior to beginning the e-consent process. This process is in compliance with the requirements of 21 CFR 11. E-consent will be done via RedCap so that study personnel may send interested, potential study participants an email with a link directly to the e-consent. The e-consent will appear as a form for the participant to read with a signature line at the bottom where participants may type in their names to indicate consent. Study personnel will plan a call with any potential study participant who chooses to remotely e-consent. On that call, study personnel may consent participants just as they would in person, while also allowing for potential participants to ask any questions before choosing to participate. As with in-person consenting, the e-consent process may take 20-60 minutes. Our goal in using e-Consent is to decrease the wait time and overall study visit length for study participants. Even if previously e-consented, participants will be required to sign a hard-copy upon their first visit to maintain on file.

For in-person consenting, participants will be provided with a signed copy of the ICF in hard copy. For e-consent, PDF versions of the signed form may be generated and a copy may be sent to both the study coordinator and the participant who has consented. Study coordinators will keep a printout copy of this PDF on file throughout the duration of the study.

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. Documentation of participation will be obtained from adult participants. Consent will be obtained by one of the study research coordinators, or other study personnel such as Dr. Leavitt. A consent form requiring signature will be presented in writing or online via e-consent. Regardless of the format of the consent form, a study personnel will verbally review the study and consent form with the potential participant - in person or over the phone. All study procedures will be thoroughly explained and all questions will be answered prior to any participant signing the consent form, either in person or on the online, RedCap e-consent.

Subjects will demonstrate informed consent by signing a consent form approved by the Institutional Review Board at CUMC. The consent form will be presented and explained to the subject by the research coordinator prior to signature. All questions raised by the subject will be answered prior to obtaining the signature.

Once enrolled, patients will be randomized using an electronic algorithm put in place by the CUMC Research Pharmacy. Only the Research Pharmacy will have access to the unblinded information until the study is completed. PPI and study personnel will be unblinded upon End of Study.

Patients may be re-screened if they screen fail as a result of the following Inclusion/Exclusion Criteria:

- Exacerbation-free (and no use of corticosteroids) for 6 weeks prior to enrollment
- BMI ≤ 40
- Uncontrolled syndrome of asthma, rhinitis, or nasal polyps

If the patient later meets these criteria, they may be re-screened. All screen failures will be documented in the Screening Log alongside successful screenings.
Patients may be re-screened if they are a screen fail as a result of any of the Lifestyle Considerations (See Section 4.3).

4.5.1 Subject Recruitment and Retention

Sixty patients with RRMS will be recruited from the Multiple Sclerosis Clinical Care and Research Center at CUMC. With approximately 900 patients seen per year, 60% of that population has a current RRMS diagnosis. This center additionally sees about 40 new patients each month. Therefore, this study does not anticipate difficulty meeting enrollment goals over the 2-year period. 100 patients will be screened, estimating that 60% of screened patients will meet eligibility.

As this study is a 3-visit commitment, the study team does not anticipate issues with subject retention. Regardless, enrollment will not be closed until all 60 participants have completed all three visits; this will ensure 60 completed participants are enrolled in this study.

Subject screening will occur as follows:

- If the patient's treating physician feels the subject may be a good fit for this study based on observations of overheating, fatigue or difficulty with exercising, s/he may discuss the trial with the patient to gauge interest.
- Patients will be referred by the patient's treating physician, many from Drs. Leavitt, Riley and De Jager, who are investigators on this protocol. All other patients will be referred either by colleagues of Dr. Leavitt, all of whom work at the Columbia University Medical Center, or from providers outside CUMC whose patients have seen study flyers and have contacted a member of the study team to express interest.
- If the patient is interested in the trial, the treating physician may have a study coordinator or other member of the study team meet with the patient to discuss the trial in further detail and answer questions. A screener (see Documents) will be reviewed with the potential participant to ensure criteria are met. If the patient meets criteria and wishes to participate, study personnel will begin the consenting process.
- Participants may be recruited via person-to-person interactions or via flyers and handouts.
- We do not anticipate recruiting vulnerable subjects, including non-English speaking subjects and persons whose capacity to consent may be questionable.

4.5.2 Screening Logs

A screening log to document all successful screenings, leading to enrollment, and all screen failures will be maintained and stored centrally at Columbia University Medical Center, in both the regulatory binder, as well as in a password-protected Excel spreadsheet.

4.5.3 Informed Consent

Subjects will demonstrate informed consent by signing a consent form actively approved and stamped by the Institutional Review Board at CUMC. The consent form will be presented to the subject and reviewed with the subject by the research coordinator or another member of the study team. Once the consent form has been reviewed and all questions raised by the subject are answered, the subject’s signature may be obtained.

4.5.4 Randomization/Treatment Assignment

If unblinding is required, the PPI may request the group assignment information of a specific participant or all study participants. This request may be made at the discretion of the PPI.

Accidental unblinding is not predicted. If this occurs, the participant will be removed from the study by the PPI.

5 STUDY INTERVENTIONS/STUDY MEDICATION/STUDY DRUG OR DEVICE

5.1 Study Medications/Interventions, Administration, and Duration

At each study visit, participants will be administered one 650mg capsule of either Acetaminophen or Aspirin, or a Placebo, which they will be instructed to take orally upon their arrival to our lab, one hour before the initiation of the exercise test. Each study visit will last approximately 1 hour. There will be no changes to this dose.

5.2 Handling of Study Medications/Interventions

In accordance with local regulatory requirements, the PPI will document the amount of investigational product dispensed and/or administered to study subjects, the amount received from the central pharmacy, and the amount destroyed upon completion of the study. The PPI is responsible for ensuring product accountability records are maintained throughout the course of the study. The unblinded pharmacist will maintain these records and provide them to the PPI upon request for review. The unblinded pharmacist will maintain the drug inventory and accountability logs for study drugs. The inventory will include details of study drug received and dispensed to subjects, batch, and ID numbers. All unused pills must be kept until reconciliation of delivery records with accountability logs have been reviewed by the PPI. After reviewing the accountability logs, the site will be instructed to destroy the remaining study medication. An accounting will be made of any drug deliberately or accidentally destroyed. Discrepancies between the amount of Aspirin, Acetaminophen, and Placebo received and dispensed drug will be reconciled.

5.2.1 Prohibited Medications/Interventions

- Medications (e.g., disease-modifying therapies) will be documented for post hoc consideration of any impact on outcomes.
- Current use of antipyretics pain medication, or APAP are prohibited during study participation (See Exclusion Criteria, Section 4.2).

Procedure for handling situation(s) when subject uses prohibited intervention during study participation is detailed in section 8: Criteria for Intervention Discontinuation

5.3 Subject compliance

N/A, as all procedures related to compliance will take place in the exercise physiology laboratory during the study visit and under the supervision of the research coordinator.

6 CLINICAL AND LABORATORY EVALUATIONS/STUDY PROCEDURES

6.1 Schedule of Activities

Evaluation	*Screening Week 0*	*Randomization/Baseline/Visit 1 Week 1 +/- 21 days*	*Visit 2 Week 2 +/- 21 days*	*Visit 3 Week 3 +/- 21 days*
Written or E- Informed Consent	*X*			
Inclusion/Exclusion Review	*X*			
Documentation of Disease/Disorder	*X*			
Medical History/Demographics	*X*			
Vital Signs/Weight/Height	*X*	*X*	*X*	*X*
Physical Examination	*X*	*X*	*X*	*X*
Neurological Examination	*X*			
Concomitant Medication Review	*X*	*X*	*X*	*X*
Exercise Test		*X*	*X*	*X*
Randomization		*X*	*X*	*X*
Dispense Study Drug		*X*	*X*	*X*
Adverse Event Review		*X*	*X*	*X*
Questionnaires		*X*	*X*	*X*

6.2 Timing of Study Activities

- Each participant will attend 3 exercise sessions scheduled on separate days separated by ≥one-week intervals (≤ 4 weeks). Exercise sessions will be scheduled at the same time of day (±1 hour), and between the hours of 10 am-5 pm to reduce the influence of circadian rhythm variability. Each study visit is estimated to take approximately 2 hours total.

- If a participant fails to adhere to any of the Lifestyle Considerations (Section 4.3), participant's study visit must be moved to another date within the allotted 1-4 week window.
- For any patients on interferon therapy, exercise sessions will not be scheduled within 48 hours post-injection, as injection-related flu-like symptoms may compromise exercise tolerance.
- If a patient experiences an MS exacerbation within 4 weeks of her/his scheduled enrollment, the study visit will be rescheduled for 4 weeks following resolution of the exacerbation (See Inclusion Criteria, Section 4.1).

6.2.1 On-Study/On-Interventions Evaluations/procedures

After a participant has been cleared to participate in the study by his/her physician and study personnel, the participant will sign the informed consent form (either a paper copy, in person, or an online e-Consent).

Study personnel will then schedule study visits with the participant. Each participant will attend three study visits separated by ≥ one-week (≤ 4 weeks). Specific procedures conducted are outlined in Section 6.1.

Exercise sessions will be scheduled for the same time of day (±1 hour), between the hours of 10 am-5 pm to reduce the influence of circadian rhythm variability. Each study visit is estimated to take approximately 2 hours total. Participants will refrain from eating for two hours prior to their session.

Study drug will be obtained from the Research Pharmacy and will be available to the participant upon arrival at Study Visit 1. Body temperature will be measured with a tympanic thermometer (right ear; Braun Thermoscan IRT).

Participants will receive one of three treatments at each session prior to the exercise test. Order of treatment will be randomized and counter-balanced, with each participant serving as his/her own control. Treatment will be administered as one capsule containing 650mg (i.e., standard adult dose for ASA and APAP) of ASA, APAP, or placebo; time of administration will be recorded. Exercise will not begin until 1 hour after the participant has taken the study drug in order to allow peak serum level to be reached. During this 1-hour waiting period, participants will complete the Hospital Anxiety and Depression Scale (HADS) and Fatigue Severity Scale (FSS) to characterize the sample; the Paffenbarger Physical Activity Scale for post-hoc evaluation of physical activity levels; and the following: day of last menstrual cycle (if female), number of hours slept prior night, any physical/outdoor activities engaged in today, presence of illness in self or family members today; and visual analog scales (VAS) of pain, fatigue, and sadness. Participants will be familiarized with Borg's ratings of perceived exertion (RPE) CR10 scale for breathing (RPEbr) and legs (RPEleg), consistent with Collett et al and the thermal sensation scale (ASHRAE scale) to be completed by participants at 60-second intervals throughout the session.

The exercise session portion of each study visit will use the following tools:

Exercise tests will be conducted by the study team 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 Vmax Encore Metabolic Cart (CareFusion Corp, San Diego, CA). Echocardiogram (ECG) monitoring is done with a twelve-lead system attached to the Vmax Encore Metabolic Cart with cardiosoft software (CareFusion Corp). Maximum aerobic fitness (VO2max) will be measured by graded maximal exercise test on a VIAsprint 150P electronic-braked cycle ergometer (CareFusion Corp). Each subject will have peak ventilatory capacity (Maximum Voluntary Ventilation, MVV) determined before exercise test via Vmax Encore System (CareFusion Corp). 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 breath-by-breath measurement of VO2. Anaerobic threshold will be determined for each subject using the V-slope technique

The exercise session portion of each study visit will occur as follows:

Each subject will complete a 5-minute resting phase followed by a 3-minute warm up and then a progressive ramped exercise test until achieving volitional fatigue. An individualized ramping protocol will be determined by a certified exercise physiologist based on subject's weight and exercise profile. This ramping protocol will be identical between study visits within subjects. Patients will maintain a cadence of 50-60 revolutions per minute (RPM) for test duration. The test is terminated when cadence drops below 40 RPM for ≥ 5 seconds, or when participant reaches volitional exhaustion in accordance with American Thoracic Society (ATS) standard test termination criteria. Throughout the test, RPE and HR will be recorded every 60 sec. Blood pressure (BP) and ear temperature will be recorded every 2 minutes. At termination, RPE, BP, and ear temperature will be recorded, as well as minute ventilation, expired oxygen (O2), carbon dioxide (CO2), watts, RER, and total time. VAS of fatigue and Global Fatigue Change (GFC) will be recorded.

To test effectiveness of blinding, participants will be asked which condition they think they were in at the end of each session.

6.2.2 Final On-Study Evaluations

The subject's final visit on study is Study Visit 3. This study visit will be identical to the previous two study visits.

6.2.3 Off-Study Requirements

There are no off-study requirements for this clinical trial.

6.3 SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

6.3.1 Informed Consent

E-Consent

We will be utilizing both in-person consenting and e-consent. E-consent will be done via RedCap, a secure online database. A copy of the e-consent form as a Redcap-generated PDF is attached to this protocol to attest to it being identical to the print-version. We will offer the e-consent to in-person participants as a way to replace the signing of a paper-based informed consent to best address the participant's needs or preferences. This is optional and a paper copy will always be available. The e-consent will show the same pages as the traditional paper consent. The potential research participant will then use this e-consent to fill out the same signature fields as the traditional paper consent form. Once the participant signs the consent and hits submit, a PDF of the completed consent will be generated and can be emailed to both the participant and the study coordinator. For both in-person and remote e-consenting, study personnel will abide by the guidelines as highlighted in the Columbia University Institutional Review Board Guidance on Electronic Informed Consent document. For e-consent, study personnel will plan a phone call with each potential participant to discuss the consent form and study in detail, allowing for each participant to ask any questions prior to signing on the online ICF. Study personnel will confirm the participant's identity by asking for the patient's full name and DOB prior to beginning the e-consent process. This process is in compliance with the requirements of 21 CFR 11. E-consent will be done via RedCap so that study personnel may send interested, potential study participants an email with a link directly to the e-consent. The e-consent will appear as a form for the participant to read with a signature line at the bottom where participants may type in their names to indicate consent. Study personnel will plan a call with any potential study participant who chooses to remotely e-consent. On that call, study personnel may consent participants just as they would in person, while also allowing for potential participants to ask any questions before choosing to participate. As with in-person consenting, the e-consent process may take 20-60 minutes. For in-person consenting, participants will be provided with a signed copy of the ICF in hard copy. For e-consent, PDF versions of the signed form may be generated and a copy may be sent to both the study coordinator and the participant who has consented. Study coordinators will keep a printout copy of this PDF on file throughout the duration of the study.

The Research Pharmacy requires at least 2 hours to prepare the study medication. With e-consenting, preparation of study drug may be hastened, allowing for shorter study visits and increasing likelihood of participation and subject retention.

6.3.2 Protocol Violations

Protocol Violations are defined by the study site’s local IRB. These include, but are not limited to:

- Using unstamped documents
- Enrolling unqualified participants

6.3.3 Medical History

Participant's medical history will be documented. Medical history includes, but is not limited to:

1. Multiple Sclerosis history
2. Psychiatric history
3. Diseases resulting in exclusion from the study

6.3.4 Concomitant Medications/Treatments

The only concomitant medications that may be documented for this study are:

4. APAP or ASA
5. Multiple Sclerosis treatment
6. Psychiatric medications
7. Pain medications

6.3.5 Protocol Amendments and Study Termination

All revisions and/or amendments to this protocol must be approved in writing by the PPI and the CIRB. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from CIRB, except where necessary to eliminate an apparent immediate hazard to a study subject.

6.3.6 Clinical Assessments

All clinical assessments will be documented on CRFs and maintained in individual participant's study folder. See Section 6.1 and 6.2 for details on study activities.

6.3.7 Questionnaires

Participants will complete the Hospital Anxiety and Depression Scale (HADS) and Fatigue Severity Scale (FSS) to characterize the sample; the Paffenbarger Physical Activity Scale for post-hoc evaluation of physical activity levels; and the following: day of last menstrual cycle (if female), number of hours slept prior night, any physical/outdoor activities engaged in today,

presence of illness in self or family members today; and visual analog scales (VAS) of pain, fatigue, and sadness.

6.3.8 Additional Evaluations

7 MANAGEMENT OF ADVERSE EXPERIENCES

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA, Office of Human Research Protection (OHRP), and Columbia University Medical Center IRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB in conjunction with the Protocol PI.

8 MANAGEMENT OF UNANTICIPATED PROBLEMS

An Unanticipated Problem (UP), per the Columbia University Medical Center IRB, is defined as: "any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:

A. unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
B. related or possibly related to participation in such research (i.e., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized."

Per CIRB reporting guidelines, UPs will be reported if they require changes to the protocol due to added risk to participants. All participants will be notified of any protocol changes and will be reconsented as appropriate. If an UP does not pose additional risk to participants and does not require changes made to the protocol, the UP may be reported as an Adverse Event.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Statistical methods recommended for the proper analysis of crossover trial data will be used (for details, see Wellek and Blettner). Our primary outcomes evaluate differences between treatment condition (ASA, APAP and placebo) with respect to (a) TTE (that is, length of time spent exercising) and (b) increase in exercise-induced body temperature (°F). Differences between pretreatment conditions (ASA, APAP, placebo) will be analysed separately by sequence group to account for possible order effects (ie, stepwise assessment of outcome differences across six possible sequences). Although significant differences in outcome variables between ASA and APAP are not anticipated, we are interested in seeing how they compare in the full analyses. A mixed-effects linear model will be used to account for repeated measurements of each outcome, period effect, sequence effect and carryover effect. Using mixed-effects linear model will enable us to model differences in outcomes both within and between patients (intrapatient and interpatient variability). If assumptions for mixed-effects linear model are not met and log transformation is not appropriate, non-linear mixed-effects models will be used. Moreover, exploratory analyses will examine potential pretreatment differences for additional outcome measures, such as physiological indices (eg, HR, BP) and behavioural self-reports (eg, RPEs, fatigue, pain).

9.2 Outcomes

9.2.1 Primary Outcome

Primary outcomes are total time to exhaustion (TTE) measured at exercise cessation and change in temperature from baseline (pre-exercise) to exercise cessation.

9.2.2 Secondary Outcomes

Secondary outcomes included patient-reported outcomes: Borg's ratings of perceived exertion scale (RPE) for breathing (RPEbr) and muscle fatigue (RPEleg) collected every 2 minutes throughout the exercise test; 10-point visual analog scales (VAS) of pain (VAS-P) and fatigue (VAS-F) measured pre- and post-exercise test; and physiological measures: heart rate (HR), systolic and diastolic blood pressure (SBP, DBP), $expO_2$, peak minute ventilation, maximum watts, and RER.

9.3 Sample Size and Accrual

In a pilot trial with 12 participants, effect sizes for both outcomes (time to exhaustion/TTE and body temperature) were very large (Cohen's d=1.45). Here, we conservatively estimated medium-sized effects (0.5) to calculate a power estimate for the proposed trial. With significance set at α=0.05 for two-tailed paired t-test, a three-arm crossover sample of 54 will yield 0.95 power to

detect differences between interventions. Our plan to enroll 60 participants allows for 10% attrition, which accounts for both participant drop-out as well as exclusion due to relapses.

9.4 Data Monitoring

All aspects of the study will be monitored by qualified individuals designated by the sponsor. Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and to the clinical files of the study subjects, and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

The monitoring of subject safety and data quality will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. A Data and Safety Monitoring Board (DSMB) appointed by the NIH/NINDS will meet at six-month intervals (or as determined by the NINDS) to review partially unblinded study data provided by the study statistician. This committee will monitor rates of adverse events and endpoints in the trial and will monitor the performance of the trial. The frequency and format of DSMB meetings, reports, and guidelines for interim analysis will be agreed upon prior to study subject enrollment.

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device. FDA, Office of Human Research Protection (OHRP), and Columbia University Medical Center IRB requirements for reporting AEs will be followed. Subjects will be monitored for AEs from the time they sign consent until 30 days following permanent discontinuation of study drug. At that point, all ongoing AEs will be followed to resolution, but no new AEs will be recorded. The IMM/DSMB will review cumulative AEs; the frequency of this review will be determined by the IMM/DSMB in conjunction with the Protocol PI.

The PPI and research team are responsible for identifying and reporting AEs and determining the relationship of the event to the study drug/study procedures. Aggregate reports blinded by treatment group, detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures, will be available from the DCC for review.

Because the potential risks are low and the trial is limited to 3 study visits (where ASA, APAP or placebo are administered in a controlled setting) that occur within a ~3 week period (i.e., there is no at-home requirement, no daily use of study drug), PI Leavitt will hold primary responsibility for monitoring the overall safety of all participants enrolled in the trial. She will work in close consultation with Co-I Stein, who will oversee the certified exercise physiologist who conducts all exercise tests, and Co-I Riley, who will ensure the suitability of all potential participants for the study. Should any of the following specific events occur, a participant would be precluded from continuing the intervention: adverse reaction to exercise test, adverse reaction to any treatment condition (ASA, APAP, placebo), patient desire to discontinue participation for any reason. If any medication-related issues are noted during the study (e.g., allergic reactions or

other adverse reaction, which is unlikely considering most of our participants will likely have used aspirin and acetaminophen already), Dr. Riley will be consulted, patient will be treated as needed, and participation in the trial will cease.

9.5 Data Analyses

All data analyses will be conducted by the study biostatistician, Dr. Amelia Boehme, who will be blinded to treatment condition until the primary analysis has been completed.

10 DATA COLLECTION, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

10.1 Data Management

Site personnel will collect, transcribe, correct, and transmit the data onto source documents, CRFs, and other forms used to report, track and record clinical research data. The DCC will monitor clinical sites to ensure compliance with data management requirements and Good Clinical Practices. The DCC is responsible for developing, testing, and managing clinical data management activities, as required, at the study sites, the CCC, and at the DCC.

The general NINDS Common Data Elements (CDE) will be used to construct data collection forms. All study data will be collected via systems created in collaboration with the DCC and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

10.2 Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets. The PPI and study coordinators will be responsible for DM and will act as the DCC for this trial.

All data will be managed in compliance with applicable regulatory requirements.

The DCC is responsible for all aspects of clinical data management, and for properly instructing key study personnel on how to collect, transcribe, correct and transmit the data onto CRFs or other data collection forms and logs.

The DCC is responsible for establishing procedures to ensure that clinical data management activities occur as required at the CCC, the CSS, and at the DCC.

All precautions to ensure patient privacy will be taken. All discussions and screening activities will be held in a private area or will be conducted by phone, with the coordinator seated in a quiet

office with only the study's coordinators being present. All patient data will be coded and all patients will be given a unique study ID number. All manipulations of samples and data will be performed using this unique number, which is separated from any subject identifier.

10.3 Quality Assurance

By signing this protocol, the Investigator agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.4 Adverse Experience Reporting

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The Site Investigator will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Any adverse events (AE), serious adverse events, or unanticipated problems involving risks to subjects or others occurring during the exercise test will be immediately reported by Dr. Leavitt to the NIH program officer according to the following timetable: deaths related to study participation (though not anticipated) will be reported no later than within 5 business days of Dr. Leavitt first learning of the death. Unexpected serious adverse events (SAEs) will be reported by Dr. Leavitt to her program officer within 10 business days of the study team becoming aware of the SAE. All AEs and SAEs that are deemed expected and/or unrelated to the study will be submitted in a summary to NIH program officer with the annual progress report. Any protocol violations that occur will be submitted with the annual progress report. All documentation submitted to the NIH PO will be prepared in accordance with NIH guidelines for documentation of Reportable Events.

In the event of any adverse events, Dr. Leavitt will work closely with Drs. Stein and Riley to ensure appropriate clinical management of the participant. Dr. Leavitt will provide written documentation, conduct a complete investigation, and follow-up on any/all possible study-related AEs. Any AEs will be reported by Dr. Leavitt to the Institutional Review Board and clinicaltrials.gov. Dr. Leavitt will be responsible for describing and adhering to the procedures for identifying, monitoring, and reporting reportable events as outlined in the Protection of Human Subjects section of this application.

Specific plan and timeframe for reporting IRB and/or ISM/DSMB actions (e.g., protocol violations, non-compliance, suspensions, terminations): Any suspension or termination of approval will include a statement of the reason(s) for the action and will be reported promptly by Dr. Leavitt to the NIH program officer within 3 business days of receipt.

An adverse event is defined as: "…an unfavorable and unintended sign, symptom, or disease associated with a subject's participation in this research trial."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

Unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks described in the protocol.

Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study.

On-line Adverse Event Reporting System

- Within **24 hours** (of learning of the event), investigators must report any Serious Adverse Event (SAE) Investigators must report all other AEs within **5 working days/7 calendar days** (of learning of the event).

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will review the SAE report. The IMM may request further information if necessary. The Online Adverse Event Reporting System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study. The IMM may determine that the Serious Adverse Event requires expedited reporting to the FDA. The DCC will prepare a Medwatch safety report for submission to the FDA. If warranted, the IMM will notify the DSMB chair. The DSMB may suggest changes to the protocol or consent form to the Study Chair as a consequence of adverse events.

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DCC in a timely fashion (within 5 working days). The events will be presented in tabular form and given to the IMM on a quarterly basis or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DCC will prepare aggregate reports of all adverse events (serious/not serious, expected/unexpected and relationship to study drug) for review. A separate report detailing

protocol compliance will also be available from the DCC for DSMB and/or site review monthly or as requested. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

10.4.1 Definitions of Adverse Events, Suspected Adverse Drug Reactions & Serious Adverse Events

10.4.1.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the subject or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures: the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Investigator.

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigators Brochure or package insert or described in the protocol. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Investigator, there is a reasonable possibility that the investigational product caused the event.

10.4.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study subject, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled "procedure" or a "treatment" is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    a. This serious criterion applies if the "disability" caused by the reported AE results in a substantial disruption of the subject's ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject (whether the subject is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an *adverse* experience, and will therefore, not be considered an SAE. An example of this would include a social admission (subject admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, suggests a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

10.4.1.3 Assessment and Recording of Adverse Events

This study will utilize the CTCAE version 4.0 coding system for adverse event recording. Adverse events reported using CTCAE will be recoded into the CRF.

Assessment of Adverse Events

At each visit (including telephone interviews), the subject will be asked "Have you had any problems or symptoms since your last visit?" in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease
6. Action taken regarding investigational product
7. Outcome

Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related: Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely: The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related: The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject. (suspected ADR)
4. Probably Related: The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state. (suspected ADR)
5. Definitely Related: The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (suspected ADR)

Recording of Adverse Events

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder.

Please Note: Serious Adverse Events (SAEs) must be reported to the CUMC IRB within 24 hours of learning of the SAE.

Entries on the AE Log (and into the online Adverse Event Reporting System) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the CUMC IRB within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)

All occurrences of Serious Adverse Events (SAEs) must be reported within 24 hours of discovery of the event. All other Adverse Events (AEs) must be reported within 5-10 business days (of discovery of the event).

Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event by a clinical site, the DCC Online Adverse Event Reporting System will immediately notify the IMM. If warranted, the IMM will notify the DSMB chair.

Serious adverse events: The investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The PPI will review the SAE report and may request further information if necessary. The DSMB may suggest changes to the protocol or consent form to the Project PI as a consequence of adverse events. The

Non-serious adverse events: Non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the IRB within 5 working days. The events will be presented in tabular form and given to the PI on a monthly basis or as requested.

The DCC will prepare aggregate reports of all adverse events (serious/not serious and expected, unexpected) for review.

11 HUMAN SUBJECTS

Documented approval from the CUMC IRB will be obtained for all participating centers prior to clinical trial start, according to ICH GCP, local laws, regulations and organization. When necessary, an extension, amendment or renewal of the CIRB approval must be obtained.

Evidence of training in responsible conduct of research shall be on file for the PI and co-investigators.

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the CUMC IRB responsible for oversight of the study. A signed consent form, approved by the CUMC IRB, will be obtained from the subject. For subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, and this fact will be documented in the subject's record.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by CIRB, the FDA, the NINDS, the OHRP, and the investigator.

11.2.1 Certificate of Confidentiality

To further protect the privacy of study subjects, a Certificate of Confidentiality will be issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to subjects.

11.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the CIRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected. If the study is terminated or suspended, the PI will promptly inform study subjects, and the IRB and provide the reason(s) for the termination or temporary suspension.

12 FUTURE USE OF STORED SPECIMENS AND DATA

- Data is anticipated for future research use. Some of all data, as applicable, will be retained by Columbia researchers for future use. 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 considered when an addition of future uses is submitted via modification. 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
- Data will be labeled during storage for future uses in the same manner as during collection (e.g., with direct identifiers, coded, de-identified, anonymous).
- Data will be physically stored in the same manner as during collection.
- Data may be released to the NIH. All data shared will be coded with no identifiers; no PHI will be released. All data will be shared via a secure file transfer or encrypted format
- The Principal Investigator and study coordinator will have access to the stored data. Other study personnel may request access to stored data from the study coordinator or PI. Some or all data/specimens will be released to a non-Columbia entity for future use and Columbia researchers will not have direct control.

13 STUDY RECORDS RETENTION

As per NIH guidelines, records will be retained for a period of three years from the date of Federal Financial Report (FFR) submission.

14 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute of Child Health and Development has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

15 PUBLICATION OF RESEARCH FINDINGS

Research findings will be published in peer-reviewed journals in a timely manner after the trial has been completed.

16 REFERENCES

Leavitt VM, Blanchard AR, Guo CY, Gelernt E, Sumowski JF, Stein J. Aspirin is an effective pretreatment for exercise in multiple sclerosis: A double-blind randomized controlled pilot trial. Mult Scler. 2018 Oct;24(11):1511-1513. doi: 10.1177/1352458517739138. Epub 2017 Oct 27. PMID: 29076760.

Kever A, Nelson KE, Aguerre IM, Riley CS, Boehme A, Lee NW, Strauss Farber R, Levin SN, Stein J, Leavitt VM. ASPIRE trial: study protocol for a double-blind randomised controlled trial of aspirin for overheating during exercise in multiple sclerosis. BMJ Open. 2020 Nov 14;10(11):e039691. doi: 10.1136/bmjopen-2020-039691. PMID: 33191260; PMCID: PMC7668379.

Appendix A: Model Informed Consent Form

Columbia University Consent Form

Protocol Information

Attached to Protocol: IRB-AAAS2529
Principal Investigator: Victoria Leavitt (vl2337)
IRB Protocol Title: Aspirin for Exercise in Multiple Sclerosis (ASPIRE)

General Information

Consent Number: CF-AACB4500
Participation Duration:
Anticipated Number of Subjects: 60

Research Purpose: The purpose of this study is to investigate the relationship between body temperature, fatigue and multiple sclerosis.
This study examines the effect of aspirin and acetaminophen on body temperature in people with MS, and the effect it may have on exercising.

Contacts

Contact	Title	Contact Information
Ines Aguerre	Coordinator	Phone: 212-305-1485 Email: mscenter_neuro@cumc.columbia.edu

Information on Research

You are being asked to join a research study funded by the National Institute of Health (NIH) because you have a diagnosis of Relapsing Remitting MS and have reported heat sensitivity. This consent form explains the research study and your part in the study. Please read it carefully and take as much time as you need.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. This trial is identified by its clinical trial number: NCT03824938.

Please ask questions at any time about anything you do not understand.

Study Procedures: If you consent to participate, you will undergo the following during the study visit:

Screening for the study will include a brief depression screener. You will complete 3 study visits, separated by at least 1 week. Study visit sessions will be scheduled between 9 am - 5 pm at the same time of day (+/- 1 hour). At each of the three study visits, the following study procedures will be repeated the exact same way.

You must first refrain from eating for two hours prior to the scheduled session. You will be randomized (similar to flipping a coin, you will have an equal, random chance of being assigned to any of the three groups) to receive either aspirin (standard dose, 650mg, provided in the form of one capsule), acetaminophen (standard dose, 650mg provided, in the form of one capsule), or a placebo (one capsule with no therapeutic effect). After having your ear temperature taken and completing brief questionnaires about your current level of pain, mood, and fatigue, you will complete a grip strength test with a study coordinator using a Dynanometer. You will then be given a pill to take. Neither you nor the investigators will know which pill you have been given until after the study is completed. You will receive a different study treatment at each visit, ensuring that you will take all three study drugs over the course of the three separate study visits. After being administered the pill, you will relax for one hour (the estimated time for aspirin and acetaminophen to reach the highest concentration in the bloodstream), before once again having ear temperature taken and completing the grip strength test again.

During the waiting period after taking the study drug, the study team will collect data and administer questionnaires. Study personnel will familiarize you with a scale that will be used during your exercise session to measure how tired you are feeling (your level of exertion). Once that has been completed, an exercise physiologist will give you an exercise test on a stationary cycle. You will wear a face mask so that we can measure your respiration during exercise. We will also continuously monitor your heart rate with EKG monitoring that will have 12-leads attached to your body, as is the same with any clinical EKG. Your blood pressure, ear temperature and feelings of exertion will be recorded every 60 seconds during exercise. The exercise test will begin with a 3-minute warm up phase and then a progressed ramped increase, which will involve cycling until you feel too tired to continue. For most people, this is not longer than about 8-12 minutes. After you finish, blood pressure, ear temperature, and exertion will be recorded again, and we will have you fill out some questionnaires on your current level of pain, mood and fatigue, as well as complete the grip strength test with the Dynanometer one last time. At the end of each session, we will ask you whether you think you were given aspirin, acetaminophen, or a placebo.

Future Use of Data

We will use your data for the research described in this form and for other future research. We will label your data with a code instead of your name. The key to the code connects your name to your samples and health information. The study doctor will keep the key to the code in a password protected computer and locked file.

Identifiers will be removed from all identifiable private information and, after such removal, the information could be used for future research studies without additional consent from you.

Any clinically relevant research results will be disclosed to you upon completion of the study.

Risks

Exercise causes exertion. To ensure your safety if you participate in the exercise condition, we will consult with your physician before enrolling you to make sure you meet all study criteria. The one-on-one exercise sessions you take part in will be overseen by a certified exercise physiologist with experience working with patients who have a variety of medical conditions. In addition to the exercise physiologist, a physician will be available for all three of your sessions.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing.

The risks of a single dose of aspirin are minimal, and because we will carefully screen for any/all conditions that may counter indicate the use of aspirin before enrollment, we do not expect any issues to arise as a result of pills taken for use in this study. Furthermore, the dosage being given is the standard dose taken for, e.g., a headache (650mg). Aspirin may increase the risk of bleeding.

The risks of a single dose of acetaminophen are also minimal, and because we will carefully screen for any/all conditions that may counter indicate the use of acetaminophen before enrollment, we do not expect any issues to arise as a result of pills taken for use in this study. Furthermore, the dosage being given is the standard dose taken for, e.g., a headache (650mg).

The risks of a stress test such as the one being conducted in this study on a stationary cycle are:
1. Feel moderate to severe chest pain.
2. Get too out of breath to continue.
3. Develop abnormally high or low blood pressure or an arrhythmia (an irregular heartbeat)
4. Become dizzy.

As heart rate, blood pressure and temperature are all being accounted for, all of these risks are minimized.

Loss of confidentiality

A risk of taking part in this study is the possibility of a loss of confidentiality. Loss of confidentiality includes having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your confidentiality. Their plans for keeping your information private are described in the 'confidentiality' section of this consent form.

Benefits

You are not expected to benefit directly from participation in this study. The ultimate benefit of this research is that we

better understand how changes in body temperature affect fatigue associated with multiple sclerosis.

Alternative Procedures

The alternative is to not participate.

Confidentiality

Any information obtained during this study and identified with you will remain confidential. Any information that may be of value to your physician for your personal treatment will be shared with your physician, unless you object to this. All information will be stored in locked files and all information in computer data bases will not have your name or any other identifying information associated with it.

The following individuals and/or agencies will be able to look at and copy your research records:
- The investigator, study staff and other medical professionals who may be evaluating the study
- Authorities from Columbia University and New York Presbyterian Hospital, including the Institutional Review Board ('IRB')
- The United States Food and Drug Administration ('FDA') and/or the Office of Human Research Protections ('OHRP')
- If this study is sponsored (money or supplies are being provided), the sponsor of this study, the National Institute of Health (NIH), including persons or organizations working with or owned by the sponsor
- Other government regulatory agencies (including agencies in other countries) if the sponsor is seeking marketing approval for new products resulting from this research.

Columbia University Irving Medical Center has recently implemented a new electronic medical record (EMR) system, which will be shared with Weill Cornell Medical Center and New-York Presbyterian Hospital and its affiliated institutions.

Your participation in this research study will be documented in our new EMR system. Medical records in this system can be viewed by authorized personnel from these institutions. Study monitors and others who provide oversight of the study may also need to access this record.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable

diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Research Related Injuries

Taking part in this research study may result in injury or harm to you. In the event of an injury resulting from your participation in this study, you should seek appropriate medical care and inform the study doctor. In the event of an emergency you should go to an emergency room.

If you are injured or harmed as a result of participating in the study and receive medical care through the New York Presbyterian Hospital (NYPH), a Columbia doctor, or any other health provider, you will be sent a bill for whatever medical care you receive. All or part of your bill may be paid by your health insurance.

Columbia University and New York-Presbyterian Hospital (NYPH) are not offering to pay you for pain, worry, lost income, the cost of your medical care or non-medical care costs that might occur as a result of your taking part in this study. However, you do not waive any of your legal rights in signing this form.

Compensation

You will be compensated $100 after the completion of all three study visits. If we pay you by check, we will ask you for your SSN or TIN number. This information will not be disclosed to any collaborators. There is no cost to you for participating in this study. Reportable payments: According to IRS regulations, compensation payments totaling more than $600 in a calendar year must be reported to the Internal Revenue Service (IRS). We will need to obtain your Social Security Number for this purpose. Reimbursement for travel or other study-related expenses are not considered compensation for tax purposes.

Voluntary Participation

Your participation in this study is completely voluntary. You can refuse to participate or withdraw at any time and such

a decision will not affect your medical care at NewYork Presbyterian Hospital, now or in the future. Signing this form does not waive any of your legal rights.

Additional Information

If you have any questions or concerns about the study, you may contact Dr. Victoria Leavitt at 212 342 1351.

If you have any questions about your rights as a subject, you may contact:

Institutional Review Board
Columbia University Medical Center
154 Haven Avenue, 1st Floor
New York, NY 10032
Telephone: (212) 305-5883

Agreement to be Contacted

May we contact you in the future for taking part in a new study related to MS or other inflammatory and neurologic diseases?

YES:_____ NO:_____
Initial Initial

Statement of Consent

I have read the consent form and talked about this research study, including the purpose, procedures, risks, benefits and alternatives with the researcher. Any questions I had were answered to my satisfaction. I am aware that by signing below, I am agreeing to take part in this research study and that I can stop being in the study at any time. I am not waiving (giving up) any of my legal rights by signing this consent form. I will be given a copy of this consent form to keep for my records.

Signatures

Participant Signature Lines

Study Participant

Print Name _____ Signature _____

Date _____

Research Signature Lines

Person Obtaining Consent

Print Name _____ Signature _____

Date _____