Dietary Flavanols and Dentate Gyrus Function

Study Protocol

Trial Registration
clinicaltrials.gov Identifier: NCT02312310;
https://clinicaltrials.gov/ct2/show/NCT02312310

New York State Psychiatric Institute

Institutional Review Board

December 17, 2019

To: Dr. Richard Sloan

From: Dr. Edward Nunes, IRB Co-Chair

Dr. Agnes Whitaker, IRB Co-Chair

Subject: Approval Notice: CONTINUATION Expedited per 45CFR46.110(b)(1)(f)(8c)

Your protocol # **7034** entitled: **DIETARY COCOA FLAVANOLS AND AGE-RELATED MEMORY DECLINE** Protocol version date 12/17/2019 has been approved by the New York State Psychiatric Institute - Columbia University Department of Psychiatry Institutional Review Board from **December 17, 2018 to October 19, 2020.**

Consent requirements:

√ Not applicable: Data Analysis Only

☐ 45CFR46.116 (d) waiver of consent for the telephone screen

☐ Signature by the person(s) obtaining consent is required to document the consent process

☐ Documentation of an independent assessment of the participant's capacity to consent is also required.

Approved for recruitment of subjects who lack capacity to consent: √ No ☐ Yes

Field Monitoring Requirements: √ Routine ☐Special: _____

✓ Only copies of consent documents that are currently approved by the IRB may be used to obtain consent for participation in this study.

✓ A progress report and application for continuing review is required 2 months prior to the expiration date of IRB approval.

✓ Changes to this research may not be initiated without the review and approval of the IRB except when necessary to eliminate immediate hazards to participants.

✓ All serious and/or unanticipated problems or events involving risks to subjects or others must be reported immediately to the IRB. Please refer to the PI-IRB website at http://irb.nyspi.org for Adverse Event Reporting Procedures and additional reporting requirements.

Cc: CU Business Office (Mars Inc)

EN/AHW/alw

Signed copy on file at IRB

Protocol Title:
Dietary Cocoa Flavanols and Age-Related Memory Decline

Version Date:
12/17/2019

Protocol Number:
7034

First Approval:
11/20/2014

Expiration Date:
10/19/2020

Contact Principal Investigator:
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Co-Investigator(s):
Scott Small
Adam Brickman, PHD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation without modifications

Division & Personnel

Division

What Division/Department does the PI belong to?
Behavioral Medicine/Psychiatry
Within the division/department, what Center or group are you affiliated with, if any?
none

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
none

Application for Continuation of Research

Status

Current Status of Study:
All research interventions were completed. Only data analysis is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.
Recruitment and procedures for the IRB Protocol #7034 - Dietary Cocoa Flavanols and Age-Related Memory Decline - is complete and only data analysis is ongoing. We have screened 2589 participants, enrolled 253, and randomized 211. Of these, 204 have completed their 12 week visit and 197 have completed their 20 week visit. 58 participants have been enrolled in the MRI arm of the study.

Funding

Have there been any changes in funding status since the prior approval?
No
Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?
Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?
No
Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?
No
Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?
Yes
Is the study covered by a certificate of confidentiality?
No

Overall Progress

Approved sample size
260
Total number of participants enrolled to date

253
Number of participants who have completed the study to date
211
Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?
No
Comments / additional information
N/A

Sample Demographics

Specify population
Healthy Adults
Total number of participants enrolled from this population to date
253
Gender, Racial and Ethnic Breakdown

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race				
Ethnic Category	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
Hispanic or Latino	13	7	0	20
Not Hispanic or Latino	107	84	0	191
Unknown (individuals not reporting ethnicity)	0	0	0	0
Ethnic Category: Total of All Subjects*	120	91		211
Racial Categories				
American Indian/Alaska Native	0	0	0	0
Asian	7	6	0	13
Native Hawaiian or Other Pacific Islander	1	0	0	1
Black or African American	17	13	0	30
White	90	70	0	160
More Than One Race	0	0	0	0
Unknown or Not Reported	5	2	0	7
Racial Categories: Total of All Subjects*	120	91		211

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)				
Racial Categories	**Females**	**Males**	**Sex/Gender Unknown or Not Reported**	**Total**
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Native Hawaiian or Other Pacific Islander	1	0	0	1
Black or African American	3	1	0	4
White	5	4	0	9
More Than One Race	0	0	0	0
Unknown or Not Reported	4	2	0	6
Racial Categories: Total of Hispanics or Latinos**	13	7		20

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
0
Did the investigator withdraw participants from the study?

Yes
Circumstances of withdrawal:
Participants failed to successfully complete the run-in portion of the study.
Did participants decide to discontinue study involvement?
No

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Neuropsychological Evaluation
✓ Collection of Biological Specimens
✓ MRI
✓ Internet-based Data Collection or Transmission

Population

Indicate which of the following populations will be included in this research

✓ Medically and Psychiatrically Healthy Subjects
✓ Adults
✓ Adults over 50

Research Support/Funding

Will an existing internal account be used to support the project?
No
Is the project externally funded or is external funding planned?
Yes
Select the number of external sources of funding that will be applicable to this study

Funding Source #1

Is the PI of the grant/contract the same as the PI of the IRB protocol?
Yes
Select one of the following
The grant/contract is currently funded
Source of Funding
Foundation
Sponsor
Mars Incorporated

Select one of the following
Single Site
Business Office
CU
Does the grant/contract involve a subcontract?
No

Study Location

Indicate if the research is/will be conducted at any of the following
✓ Other Columbia University Medical Center Facilities
This protocol describes research conducted by the PI at other facilities/locations
No

Lay Summary of Proposed Research

Lay Summary of Proposed Research

In our previous study, we found that consuming a diet rich in cocoa flavanols (900 mg per day, according to the older assay used to quantify cocoa flavanols) for three months improved imaging and cognitive measures of memory. We are conducting this research to confirm and extend the finding that a dietary flavanol intake improves age-related memory decline.

In this study, we will recruit 260 subjects, 200 of whom will meet inclusion and exclusion criteria. Subjects will be screened by phone and then in person to ensure they meet inclusion criteria. They will complete a medical history questionnaire. We will also conduct an optional MRI sub-study. Subjects who express interest will complete a claustrophobia questionnaire, and will be screened for conditions that contra-indicate MRI studies. The Montreal Cognitive Assessment (MoCA) will also be administered before final eligibility is determined. Subjects will be randomized to one of four groups, the members of which will be assigned a specific daily cocoa flavanol intake amount (0mg, 225mg, 400mg or 650mg per day +/= 10%* per day), respectively. Subjects will take the cocoa flavanols for 12 weeks during which they will complete neuropsychological testing at week 4 of the 12-week period. After the 12 weeks, subjects will return for follow-up assessment of neuropsychological testing and MRI, if they participate in the optional MRI sub-study. Eight weeks after the last cocoa flavanol intake, subjects will complete a final neuropsychological testing.

*As a food product with natural variation, cocoa extract CF values denoted throughout this protocol are subject to a variance of +/-10%. These values, based on a new and different assay for cocoa flavanols, correspond to 300 mg, 600 mg, and 900 mg of cocoa flavanols derived from an older assay no longer used by Mars Symbioscience.

Background, Significance and Rationale

Background, Significance and Rationale

The prefrontal cortex[1] and the hippocampal formation[2] are two brain areas that are affected by aging and are thought to contribute to age-related memory decline[3]. The hippocampal formation itself is a circuit made up of interconnected regions[4]. Each region houses a population of molecularly and functionally distinct neurons, which accounts for why individual regions are differentially affected by aging and disease[4]. In humans[5, 6], non-human primates[7, 8], and rodents[7, 9, 10] the dentate gyrus (DG) is the region of the hippocampal circuit that has shown the most consistent age-related changes using various indicators of functional integrity. Nevertheless, because these observations are only correlational, a question remains as to whether DG dysfunction directly contributes to age-related memory decline and whether an intervention that improves DG function will ameliorate memory decline in older subjects.

A recent study in young mice showed that oral consumption of epicatechin, a dietary flavanol, improved DG and memory function and that this improvement was enhanced by aerobic exercise[11]. We hypothesized that a dietary supplement high in epicatechin, perhaps together with exercise, would enhance DG function in older humans, and that this enhancement would mediate an improvement in cognitive performance.

Using a variant of fMRI that relies on steady-state contrast enhancement to generate basal maps of cerebral blood volume (CBV)[12], we identified age-related decline DG dysfunction and distinguished it from regions of the hippocampal circuit that are associated with Alzheimer's disease (AD)[7,9,13].

Next, in anticipation of an intervention study, we developed a cognitive task that localizes, at least in part, to the site of age-related CBV decline. This task, the modified Benton Visual Retention Test (ModBent), selectively correlated with DG CBV. Moreover, ModBent performance worsens with age, at a rate of approximately 220ms per decade (β=22.31, $p<0.001$).

We then designed a double-blind 3-month intervention study in which healthy but sedentary subjects, between ages of 50-70, were randomly assigned to one four experimental groups: Subjects either received a daily dietary supplement of high flavanols (900 mg per day, according to the older assay used to quantify cocoa flavanols) enriched in epicatechin[14], with or without a regimen of aerobic fitness; or a dietary supplement of low flavanols (45 mg per day), with or without a regimen of aerobic fitness training. The aerobic fitness regimen consisted of 1 hour per day of aerobic exercise, four days per week. All subjects were imaged with CBV-fMRI and were evaluated with the ModBent at baseline, and then a second time at the end of the study. Besides CBV-fMRI and ModBent as the primary outcome measures, aerobic capacity (VO2max) was included as a secondary measure to determine whether the aerobic fitness regimen was effective.

Results revealed that the dietary intervention had a significant effect on ModBent performance, independent of exercise ($t=2.17$, $p = .038$). Unexpectedly, exercise had no effect on VO2max and so the exercise intervention was considered a treatment failure.

Our aim in this current proposal is to replicate this finding and to further explore the effects of different daily intake amounts of the flavanol dietary supplement and the time course of these effects.

Specific Aims and Hypotheses

Specific Aims and Hypotheses
Specific Aim: To confirm and extend the finding that a dietary cocoa flavanol intake improves age-related memory decline.
In our previous study, we found that consuming a diet rich in cocoa flavanols (900 mg per day, according to the older assay used to quantify cocoa flavanols) for three months improved imaging and cognitive measures of memory decline.
Two questions remain unknown:
A) the time course of the effect.
B) Whether different daily intake levels of the flavanols will produce different effects on cognitive and imaging outcomes.

We plan on studying both questions by testing four different daily intake amounts of cocoa flavanols: 0mg, 225 mg, 400mg and 650 mg.

Description of Subject Population

Sample #1

Specify subject population
Healthy adults
Number of completers required to accomplish study aims
200
Projected number of subjects who will be enrolled to obtain required number of completers
260
Age range of subject population
50-75

Gender, Racial and Ethnic Breakdown

As with past studies carried out in the Columbia University Medical Center campus (17.4% African American, 10.5% Hispanic, 16.4% Asian, 48% White and 7.7% Unknown) the population of New York City is correspondingly ethnically diverse.

	African American	Hispanic	Asian or Pacific Islander	White	Other or unknown	Total
Female	21	13	20	57	9	120
Male	14	8	13	39	6	80
Total	35	21	33	96	15	200

Description of subject population
260 subjects will be recruited, ages 50-75. Subjects will be recruited from the community within New York City through many modalities, including flyers, announcements, and postings on websites and in newsletters. These approaches to recruitment have been highly successful in the past. As with past studies carried out in the Columbia University Medical Center campus (17.4% African American, 10.5% Hispanic, 16.4% Asian, 48% White and 7.7% Unknown) the population of New York City is correspondingly ethnically diverse. Sixty percent of the subjects in each group will be female.

Recruitment Procedures

Describe settings where recruitment will occur
Subjects will be recruited by posting and passing out flyers and brochures at Columbia University campus and the local community. We also will purchase print ads in local newspapers. We also plan to publish the ads in Craig's List and on Facebook. These internet ads will be identical to the print ads. In addition, we will use radio broadcast in the form of public service announcements and paid advertisements on local radio stations. Moreover, subjects will be recruited by tabling at health-related and community events. We will also post our study on Research Match and RecruitMe, Columbia University Medical Center's recruitment registry. We will also utilize a market mailing approach. Letters will be sent to appropriately aged potential subjects randomly selected from commercial lists.
How and by whom will subjects be approached and/or recruited?
Names and titles of persons designated to obtain consent and/or recruit are found on "Persons designated to discuss and document consent" section of the PSF. Subjects will be approached and/or recruited by our IRB approved recruitment material and events.
How will the study be advertised/publicized?

Subjects will be recruited by posting and passing out flyers and brochures at Columbia University campus and the local community. We also will purchase print ads in local newspapers. We also plan to publish the ads in Craig's List and on Facebook and Twitter and our study webpage. These internet ads will be identical to the print ads. Audiovisual advertisements will be posted to our Facebook and Twitter and our study webpage as well. We will also use radio broadcast in the form of public service announcements and paid advertisements on local radio stations. We will also utilize a market mailing approach. Letters will be sent to appropriately aged potential subjects randomly selected from commercial lists. In addition, we will use Research Match and CUMC's RecruitMe, those who expressed interest will be contacted by our research staff. Subjects will additionally be recruited by tabling at health-related and community events. Research staff will oversee the promotional tables and provide interested subjects with a short introduction to the study. Subjects will be screened by a study coordinator during a telephone call. Those who meet enrollment criteria will be scheduled for an appointment during which the study will be described in detail and informed consent will be obtained. Subjects who fail to meet the study's inclusion and exclusion criteria will not be permitted to continue in the study.

Do you have ads/recruitment material requiring review at this time?

No
Does this study involve a clinical trial?
Yes
Please provide the NCT Registration Number
NCT02312310

Concurrent Research Studies

Will subjects in this study participate in or be recruited from other studies?
Yes
Describe concurrent research involvement
Subjects previously screened for other studies conducted by the Behavioral Medicine program at Columbia University Medical Center who were marked as ineligible will be contacted by phone and asked if they are interested in this particular study. Only those subjects who consented to being re-contacted if they become eligible for another study in the future will be asked to participate.

Inclusion/Exclusion Criteria

Name the subject group/sub sample
All Subjects
Create or insert table to describe the inclusion criteria and methods to ascertain them

INCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
1. Signed and dated informed consent obtained before any trial-related activities. (Trial-related activities are any procedure that would not have been performed during normal management of the subject).	Telephone Screen
2. Healthy Male or Female subjects. (Females must be post-menopausal)	Telephone Screen
3. Age between 50 and 75 years, both inclusive.	Telephone Screen
4. Body mass index between 18.0 and 35 kg/m^2, both inclusive.	Telephone Screen

Create or insert table to describe the exclusion criteria and methods to ascertain them

EXCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
GENERAL	
1. Currently undergoing medical treatment, including prescription drugs/medication.	Medical History Interview
2. Clinically significant abnormal hematology, biochemistry, urinalysis, or coagulation screening tests, as judged by the Investigator.	Medical History Interview
3. History or presence of cancer (except basal cell skin cancer or	Medical History Interview

squamous cell skin cancer), or any clinically significant cardiovascular, respiratory, metabolic, renal, hepatic, gastrointestinal, endocrinological (with the exception euthyroid struma), haematological, dermatological, venereal, neurological, psychiatric diseases or other major disorders as judged by the Investigator.	
4. Seated blood pressure at screening (after resting for 5 min in seated position) outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic (excluding white-coat hypertension; therefore, if a repeated measurement shows values within the range, the subject can be included in the trial) and/or resting supine heart rate outside the range 50-90 beats per minute.	Measurement taken at consent before eligibility is determined
5. Current Depression or Anxiety Symptoms using PHQ-8 and GAD-7. PHQ-8 score >= 10 and/or GAD-7 score >= 10 are excluded. (Past history of disorders not exclusionary)	Interview
6. Currently taking SSRI medications for any reason	Interview
7. Heart Diseases.	Medical History Interview
8. Hepatitis B or C positive status.	Medical History Interview
9. HIV positive status.	Medical History Interview
10. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction.	Medical History Interview
11. Use of non-prescription medication, herbal products or nutritional supplements during the study, and within the last 4 weeks before the start of the study (screening), as judged by the Investigator; occasional use of aspirin, ibuprofen, acetaminophen is permitted.	Interview
12. Adherence to a vegan or vegetarian diet or to specialty/uncommon diets.	Interview
13. Food Allergies to tree nuts, soy, cocoa and cocoa-containing products.	Interview
14. People who choose to avoid caffeine intake.	Interview
15. Current or history of alcoholism or drug/chemical abuse as per Investigator's judgment.	Medical History Interview
16. Hormone Replacement Therapy; Currently pregnant; Pregnant or lactating within past 6 months; Hormonal birth control (pill).	Interview
17. Smoking.	Interview
18. Unwilling to have blood drawn or anxiety/nausea during a blood draw.	Interview
19. Uncomfortable completing memory and attention tasks in the English language	Interview
20. Montreal Cognitive Assessment (MoCA) score less than 26.	Montreal Cognitive Assessment
21. Inability to swallow study capsules	Interview (at Consent)
22. Did not complete the two weeks Run-In Period (Participants who	Run-In Period

missed more than 2 intake occasions out of 14 days (28 occasions total) or if there are > 8 capsules left in the bottle after the two weeks will be excluded).	
MRI RELATED	
1. Cardiac Pacemaker	Interview
2. Internal Pump	Interview
3. Insulin Pump	Interview
4. Tattoo eyeliner	Interview
5. Wire sutures	Interview
6. Internal Metal Objects	Interview
7. Metal Slivers in Eye	Interview
8. Prosthesis	Interview
9. Hearing Aid Implants	Interview
10. Neurostimulator	Interview
11. Metal Fragments	Interview
12. Brain Aneurysm Clips	Interview
13. Vascular Clips	Interview
14. Breast Expander	Interview
15. Vena Cava Filter	Interview
16. Heart Valve	Interview
17. Metal Stents	Interview
18. Asthmatic symptoms within the past 3 years	Interview
19. Sickle Cell Disease	Interview
20. Kidney Disease	Interview
21. Pregnant	Interview
22. Claustrophobic	Interview
23. Wheelchair bound	Interview
24. Machinist or ever worked with heavy metals	Interview
25. Contraindication to Gadolinium, including prior adverse reaction to gadolinium, past or current history of severe breathing difficulty that has been treated by a physician (e.g. asthma, COPD, etc) and sickle cell disease. History of renal impairment or estimated glomerular filtration rate <30 L/min.1.732m2 is also exclusionary	Interview; Glomerular filtration rate assessed with creatinine via StatSensor monitor
26. Had more than one previous MRI scans with Gadolinium	Interview

Waiver of Consent/Authorization

Indicate if you are requesting any of the following consent waivers
Waiver of consent for use of records that include protected health information (a HIPAA waiver of Authorization)

No
Waiver or alteration of consent
Yes
Waiver of documentation of consent
No
Waiver of parental consent
No

Consent Procedures

Is eligibility screening for this study conducted under a different IRB protocol?
No
Describe procedures used to obtain consent during the screening process
Subjects will be screened by a study coordinator during a telephone call. Those who meet enrollment criteria will be scheduled for an appointment during which the study will be described in detail and informed consent will be obtained. At this appointment, a medical history will be taken and subjects who fail to meet the study's inclusion and exclusion criteria will not be permitted to continue in the study.
Describe Study Consent Procedures

Informed consent will be documented with a signed consent statement giving a description of the study in detail. In the Consent Form and through discussion with a research assistant, subjects will be advised fully of the study procedures, time required, the possible risks and benefits of participation, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Investigators. During consent, if the subject asks or if a Research Assistant feels there is an issue the Investigators should clarify with the participant, the Research Assistant will immediately contact Dr. Richard Sloan, or one of the Co-Investigators. At the consent, subjects' height, weight, blood pressure and body composition will be measured to determine BMI. To assess the BMI and body composition of all subjects, we will perform bioelectrical impedance analysis (BIA). BIA will be conducted with a body fat analyzer (Bodystat 1500, Vacumed, Ventura California) by applying a constant low level alternating electrical current to the individual via electrodes on a scale that subjects step on.
Additional Consent Procedures for MRI (The MRI is an optional sub-study, only those that agree to have the MRI will go through the following procedures)
Eligible subjects will then come in for a consent session with a research assistant. The subject will read through the Consent Form which contains specific information about risk factors for reactions to gadolinium and reported adverse reactions. Subjects may contact our study physician with any questions or concerns they may have regarding gadolinium. The subject will complete a Pre-Gadolinium Assessment of Risk form, which will be reviewed and signed by our study physician, Dr. Scott Small. The Pre-Gadolinium Assessment of Risk form gathers pertinent medical information including a history of kidney or liver disease, hypersensitive reactions to contrast agents or related allergens. Subjects who have any MRI or gadolinium-related contraindications will not be considered eligible. Eligible subjects will meet with a registered nurse, an MD fellow, the attending physician, or the Director of the MRI, who will present the

separate consent form for the MRI and gadolinium and obtain the subject's signature in person. Subjects will also complete a Gadolinium Quiz before the MRI scan.

Indicate which of the following are employed as a part of screening or main study consent procedures
✓ Consent Form

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following
Telephone screens.
Explain why your research can not be practicably carried out without the waiver or alteration
It will be very impractical for our study to ask to the subjects to come to our office to sign a consent form and
then proceed to establish if they are eligible.
Describe whether and how subjects will be provided with additional pertinent information after participation
N/A

Persons designated to discuss and document consent

Select the names of persons designated to obtain consent/assent
Girgis, Ragy, MD
Kegeles, Lawrence, MD
Koorathota, Sharath
Lauriola, Vincenzo
Sloan, Richard, PHD
Steinberg, Louisa, MD
Stella, Chloe
Uniacke, Blair
Type in the name(s) not found in the above list

Study Procedures

Describe the procedures required for this study

Study Protocol Summary:
Interested subjects will be screened by a study coordinator during a telephone call. Those who meet enrollment criteria will be scheduled for an appointment and provide informed consent. Participants' height, weight, and blood pressure will be measured. They will be asked to fill out the Baecke Physical Activity Questionnaire and answer the General Health Question "How would you describe your general health?". Next, participants will be shown a sample of the study capsules and asked "Are you able to swallow this capsule?" Participants answered "No" will be excluded from the study. The Montreal Cognitive Assessment

(MoCA) will also be administered. If the participant's score is 26 points of higher, the first neuropsychological testing will be scheduled. This is a pre-baseline testing to wear off any novelty effects. Subjects will also go through a Run-In period in which they will take placebo-containing capsules for two weeks**.** Then, the first set of appointments will be scheduled which consists of a neuropsychological testing session and an MRI scan (optional). Participants' body composition will also be measured at this time. Subsequently, they will be randomized to take one of four daily intake amounts of cocoa flavanol, 0 mg, 225 mg, 400mg or 650mg, per day for 12 weeks. Subjects will be scheduled for one neuropsychological sessions after 4 weeks of taking the cocoa flavanols. Then at the end of the 12 week period, the second set of appointments will be scheduled (Neuropsychological Testing and the optional MRI scan). Participants' weight and body composition will also be measured. Finally, 8 weeks after the last intake of cocoa flavanols, participants will complete a final neuropsychological testing session and a final weight and body composition measurements will be taken.

Initial screening:
Subjects will be screened by a study coordinator during a telephone call. The telephone screen includes medical history and diet questions. Those who meet enrollment criteria will be scheduled for an appointment during which the study will be described in detail, informed consent will be obtained.
The MoCA will be administered by a trained research assistant after consent is obtained but before final eligibility is determined. The RA will not inform the subject of the result. If the subject's score is < 26 (cutoff score), the RA will contact the study's neuropsychologist, Dr. Adam Brickman to discuss the results. The RA will then inform the subject of ineligibility and will refer them to Dr. Adam Brickman to discuss the score if needed.

Run-In Period:
All participants will be instructed to take two placebo-containing capsules twice a day at meals for two weeks. This is a way to test compliance before randomization of subjects to the 12 weeks test period.

At the beginning of the Run-In Period, participants will receive the placebo-containing capsules in a sealed HDPE bottle, topped with an electronic Medication Event Monitoring System (MEMS) Cap manufactured by MWV Switzerland Ltd. The MEMS Cap registers the date and time the bottle is opened and closed. The research assistant will explain how the device works and will set up a user profile on MEMS Cap's website using only the participant's subject ID. At the end of the Run-In Period, the research assistant will collect the bottle and cap back from the participant and download the data using a MEMS Cap reader and transfer the data to MWV's secured centralized database called medAmigo.

To address any information security concerns, the profile will only use the participant's subject ID to protect the participant's identity. Only the research assistants will have access to the participant's profile. In this way, we can monitor participants' compliance throughout the study.

Participants will be excluded after the Run-In period if they miss more than 2 intake occasions out of 14 days (28 occasions total) measured by MEMS Cap or if there are more than 8 capsules left in the bottle.

Optional MRI (Magnetic Resonance Imaging) Procedures:
Potential subjects will be initially screened on the phone by trained research assistants for MRI eligibility with a medical history questionnaire that addresses MRI and gadolinium-related contraindications (e.g.

cardiac pacemaker, internal pump, kidney disease, liver disease, and any history of allergic reactions to medication.) Participants will be asked if they had any previous MRI scan and about MRI-related intravenous injections with the purpose of contrast agent administration. In the case that participants recall an IV they will be asked if the contrast agent used was Gadolinium. Participants with more than one MRI scan with the use of Gadolinium will be excluded from the study.

Eligible subjects will then come in for a consent session with a research assistant. The subject will read through the primary consent form, which contains a brief overview of the MRI procedure and gadolinium. The subject will complete a Pre-Gadolinium Assessment of Risk form, which will be reviewed and signed by our study physician, Dr. Scott Small. The Pre-Gadolinium Assessment of Risk form gathers pertinent medical information including a history of kidney or liver disease, hypersensitive reactions to contrast agents or related allergens. Subjects who have any MRI or gadolinium-related contraindications will not be considered eligible. Eligible subjects who have read the consent form and completed the Pre-Gadolinium Assessment of Risk form will sign and date the consent form. Subjects will also complete the NYSPI MRI Metal Screening questionnaire. The questionnaire asks specifically about metallic implants and past experiences with metal to further ascertain any possible risks the person may incur by entering the scanner. If any metallic implants are detected that are unsuitable for the scanner, that subject will not be included in this part of the study.

The MRI scan uses an exogenous contrast agent called gadolinium which increases signal to noise ratio during MRI scanning allowing improved image quality. On the day of the primary consent, subjects will be given a gadolinium fact sheet written by Dr. Scott Small. The fact sheet includes a description of the type of gadolinium we use and its possible side effects and contraindications. If subjects have any questions regarding the use of gadolinium, we will provide the subjects with Dr. Small's contact information. In addition, they will be able to ask questions of the registered nurse, fellow, or attending physician who will administer the gadolinium.

On the day of the MRI, the subject will meet with a registered nurse, fellow, or attending physician who will provide the subject with a detailed description of the MRI procedure including the use of the contrast agent gadolinium, its possible side effects and contraindications. The subject will complete a quiz as a check that the subject fully understands the use of gadolinium, possible side effects and contraindications. A registered nurse, an MD fellow, the attending physician, or the Director of the MRI Unit, will then present the separate consent form for the MRI and gadolinium and obtain the subject's signature in person. The registered nurse, fellow, or attending physician will review both the MRI questionnaire prior to scanning and the results of the creatinine test (see below) prior to gadolinium injection.

Before the MRI scan is started, a blood sample will be taken and results for serum creatinine level will be used to estimate glomerular filtration rate (eGFR). Serum creatinine, along with age, gender, and race will be used to derive an estimated glomerular filtration rate according to a published calculator available at http://www.nephron.com/MDRD_GFR.cgi. Any subject with a history of renal impairment or eGFR < 30 mL/min/1.73m2 will be excluded from receiving an intravenous injection of the compound gadolinium.

Subjects with acceptable GFRs will receive an intravenous injection of a Gadolinium compound, to help visualize the blood supply to the brain. Gadolinium compounds are contrast agents that dissolve in blood and are eliminated by the kidneys. These compounds are routinely used as part of standard MRI tests across

the world and it has rare side effects. We use the macrocyclic variant of Gadolinium, Dotarem (gadobenate meglumine), in which data suggest that unlike the linear Gadolinium variant, the macrocylic variant is not retained in the brain regardless of the number of Gadolinium administrations. [16,17]. People with allergies or known sensitivities to contrast agents will not be injected with gadolinium.

For female subjects only: before being scanned, they will be asked to sign a pregnancy test release form stating they have been warned of potential risk to an unborn child/fetus and have been offered a pregnancy test to determine if they are pregnant before being scanned and have chosen to decline. Because the recruiting age range is 50-75 years old and we have screened for post-menopausal and pregnancy status, we will not require every female subject to take a pregnancy test. For subjects who refused to sign the release form, pregnancy tests will be provided and the registered nurse, fellow, or attending physician will sign off on the results of the pregnancy test.

MRI scans will be acquired at two time points: baseline and following the 12-week cocoa consumption period. Subjects will be asked to consume their last cocoa flavanol capsules between 12 and 24 hours prior to the scheduled follow-up MRI scan.

One of the main advantages of MRI is that patients and subjects can be safely imaged repeatedly over time. This is true also for gadolinium enhanced MRI, as used in our protocol (for example, Fillippi et al. Brain, 1998, 121:2011-2020). To detect a change in CBV caused by neurogenesis using MRI, images must be acquired both before and after exposure to a neurogenic stimulant – in this case, flavanols. Therefore, subjects enrolled will be imaged twice, once immediately prior to the start of the dietary flavanols and once immediately following the last consumption of cocoa flavanols. In addition to the gadolinium scan, standard MRI sequences will be acquired, such as 3D T1-weighted high-resolution anatomical images, fluid attenuated inverse recovery (FLAIR) T2-weighted scans, and a diffusion tensor imaging scan (DTI) used to track the motion of water within a voxel.

On the day of the MRI, if the subject does not want to receive gadolinium, we will ask the subject if they are willing to have the MRI scan without the contrast agent. The sequences we will acquired will be the T1-weighted high-resolution anatomical images, fluid attenuated inverse recovery (FLAIR) T2-weighted scans, and a diffusion tensor imaging scan (DTI).
The MRI scans will be sent to a neuroradiologist to be examined for evidence of any abnormalities within 1 month of the scan**.** Letters will be distributed to all participants following each scan indicating the significant, insignificant, or minor findings. Copies of the MRI Report can be sent to the participant's physician if requested. If the clinical reading suggests evidence of significant abnormalities (at the discretion of the radiologist), the PI will be notified immediately, and feedback will be provided to the participant.

NYSPI MRI Unit Safety Monitoring Procedures

An MD or RN, who has been approved by Dr. Lawrence Kegeles, the Medical Director of the NYSPI MRI Unit, will be covering each scan to monitor participants for serious allergic reaction. The covering MD/RN will be BLS certified and will be trained in the use of an epinephrine auto-injector ("epi pen"). An epi pen will be provided by the MRI unit and kept on the unit.

The study staff will also present a gadolinium study form to the covering MD/RN. The covering MD/RN will verify that the subject meets the creatinine clearance inclusion criterion and will exclude subjects who do not or for whom the completed gadolinium form is not presented. For subjects who meet eligibility criteria, the covering MD/RN will place an IV catheter with t-connector before the scan and remove the catheter following the end of the scan.

The participant's weight will be measured and communicated to the covering MD/RN and MRI technologist. The MRI technologist will use this information to determine the volume dose of gadolinium solution and verify the dose with the covering MD/RN prior to preparing it.

The covering MD/RN will be present at the time of gadolinium injection and will monitor the participant beginning at least 5 minutes prior to the time of injection until at least 10 minutes following injection.

In case of Emergency, the covering MD/RN will administer epinephrine via epi pen if indicated and provide supportive care as indicated including CPR and oxygen until arrival of emergency response personnel.

In case of an arrest the MRI unit staff will call
• the NYSPI rapid response team
• the NYPH code team
• 911the MRI unit director and medical director

In case of an arrest MRI unit staff will disengage the MRI scanner bed and move the participant on the scanner bed out of the scanner room. MRI unit staff will transport the basement level crash cart to the MRI unit.

In case of resolution of the emergency (e.g. emesis in the scanner) the study may resume.

Neuropsychological Testing:
A standardized battery of computerized and pencil-and-paper neuropsychological tests will be administered to measure overall cognitive functioning and change in cognition. We will use three memory tests as primary outcome measures. One is a serial list learning and memory task and the other two are computerized memory and cognition tasks. The entire battery of tests takes approximately 1 hour to complete.

These are all standardized tests commonly used in clinical practice. Gross cognitive function and intelligence measures will be administered at baseline only. All other measures will be given at all testing visits; alternate forms will be used where applicable.

Randomization:
Subjects who complete/neuropsychological testings and the MRI (optional) will be randomized to one of four groups, the members of which will be assigned a specific daily cocoa flavanol intake amount (0mg, 225mg, 400mg, or 650mg per day), respectively.

Dietary Intervention:

Daily, each subject will consume either two cocoa flavanol-containing capsules twice a day with a meal or two placebo-containing capsules twice a day with a meal. The capsule material for both types of capsule is identical and gelatin-based. All test materials are food-grade materials, manufactured and packaged under current Good Manufacturing Practices, or cGMP.
The cocoa flavanol-containing capsules are formulated to provide a total of 0 mg, 225 mg, 400 mg, or 650 mg of cocoa flavanols per 4-capsule serving. Each capsule contains 5-16 mg of caffeine, depending on daily intake of cocoa flavanols. Subjects will be randomized into one of four groups, the members of which will be assigned a specific daily cocoa flavanol intake amount.

a. 0 mg cocoa flavanol-free control capsules**:**
Ingredients: microcrystalline cellulose, gelatin, artificial coloring, magnesium stearate, stearic acid, silica, and titanium dioxide.
b. 225 mg cocoa flavanol capsules:
Ingredients: Cocoapro™ cocoa extract, microcrystalline cellulose, gelatin, stearic acid, silica, croscarmellose sodium, magnesium stearate and titanium dioxide.
c. 400 mg cocoa flavanol capsules:
Ingredients: Cocoapro™ cocoa extract, microcrystalline cellulose, gelatin, stearic acid, silica, croscarmellose sodium, magnesium stearate and titanium dioxide.
d. 650 mg cocoa flavanol capsules:
Ingredients: Cocoapro™ cocoa extract, microcrystalline cellulose, gelatin, stearic acid, silica, croscarmellose sodium, magnesium stearate and titanium dioxide.

Food Safety
Both, the cocoa flavanol-containing capsules and the placebo-containing capsules will be provided by MARS Inc., USA. MARS Inc. is a USDA-licensed food manufacturer and all test materials are food-grade materials, manufactured and packaged under current Good Manufacturing Practices, or cGMP.
Quality Control/Adherence
Virtually all studies suffer from substantial attrition. To help maintain participant retention, the following activities will be implemented:
Compliance Monitoring:
The MEMS Cap used during the Run-In Period will also be used during the 12 weeks of intervention to monitor compliance. Participants will also be asked to fill out a daily intake report form every time they take the capsules to keep track of their routine.
The Research Assistants (RA) :
A research assistant is assigned to each subject after consent. The RA will be trained in behavioral techniques designed to promote adherence, including weekly phone or email contact to remind and to encourage the consumption of the cocoa flavanols. The RA will follow subjects throughout the protocol, letting them know when it is time to schedule testing sessions. The RA will meet with the subject at each testing session to explain the procedure and to collect daily intake report forms.
Imaging Data Acquisition for the Optional MRI sub-study:
Using a Philips 3.0 Tesla scanner, T1 weighted images (TR, 20mg; TE, 6mg; flip angle, 25 degrees; in plane resolution, 0.86 mm/0.86 mm; slice thickness 3mm) will be acquired perpendicular to the hippocampal longaxis before and 4 min. after i.v. administration of the contrast agent gadolinium (0.1mmol/kg). To generate CBV maps, the precontrast image will subtracted from the postcontrast image, and the difference in the sagittal sinus, which serves as an estimate of the image intensity change of 100% blood, will be

recorded. The subtracted image will then be divided by the difference in the top % of the pixels measured from the sagittal sinus and multiplied by 100, yielding relative CBV maps.

In addition to the gadolinium scan, standard MRI sequences will be acquired, such as 3D T1-weighted high-resolution anatomical images, fluid attenuated inverse recovery (FLAIR) T2-weighted scans, and a diffusion tensor imaging scan (DTI) used to track the motion of water within a voxel.

Medical Monitor:
We've identified Dr. Peter Shapiro, Professor of Psychiatry and Associate Director of Consultation-Liaison Psychiatry Service & Behavioral Medicine, as the Medical Monitor of the study. Although the intervention capsules themselves are expected to pose low risk, the intervention cocoa flavanol levels are double blinded from all study staff and investigators. As a result, we are including a monitor who will have access to the blinded treatment levels information and will independently report to the IRB in the event of unexpected symptoms or medical conditions during individuals' participation in the study. The Medical Monitor is responsible for overseeing the safety of the research and report observations/findings to the IRB of Record. He will review all unanticipated problems involving risk to participants or others associated with the protocol and provide an unbiased written report of the event to the IRB of Record. The Medical Monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The Research Monitor shall have authority to stop the research protocol in progress, remove individual human subjects from the study, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. The Medical Monitor is responsible for promptly reporting their observations and findings to the IRB.

Text Message Reminders:
In order to increase compliance in between study visits, participants will receive text message reminders that will be sent through our password-protected database. The database will be programmed to automatically send text messages to subjects' mobiles phones at specified times via Reminder Services Inc. Reminder Services Inc. is an approved Columbia vendor and has signed a Business Associate Agreement with CUMC Privacy Officer. No personally identifiable information will be sent to Reminder Services Inc. The text messages will remind subjects of study visit appointments and reminders to complete questionnaires. The message will prompt subjects to reply with a number answer indicating whether they confirm or need to reschedule the appointment. If subjects indicate that they need to reschedule, research assistants will contact subjects directly to reschedule the appointments. The nature of the study will not be revealed nor will any aspect of the study procedures be discussed through text messages. Participants may choose to opt in or opt out of the text message reminders at any time throughout the study.

You can upload charts or diagrams if any

Blood and other Biological Samples

Please create or insert a table describing the proposed collection of blood or other biological specimens

A blood sample of 41 ml will be taken prior to and after completion of the dietary interventions. Blood will be drawn at the MRI scan before the 12 week consumption period, after the 12 week period and then 8 weeks after the cocoa flavanol washout period.

If time constraints prevent blood collection at either scan, qualified research staff may collect the samples at a separate session.
The table below indicates the purpose of the blood draw.

Assays: (41ml total)	**Purpose**
Creatinine	Confirm kidney function
Hormones (FSH, progesterone, estradiol, testosterone & Anti-Mullerian Hormone)	To observe hormonal effects of the intervention.
CCL11	Determine relationship to dentate gyrus function
Theobromine	Confirm compliance
Inflammatory markers (IL6, TNF, CRP, & HMGB1)	Determine relation of the interventions to the effect of inflammation on health.
Metabolism	Check for normal metabolism by looking at fasting glucose and insulin levels

Assessment Instruments

Create a table or give a brief description of the instruments that will be used for assessment

Screening (30 minutes): Subject will complete the Montreal Cognitive Assessment (MoCA) to check gross cognitive ability.

Baecke Physical Activity questionnaire (10 minutes): In our previous study, we used this questionnaire as a measure of sedentary activity. We want to keep this as a measurement to compare physical activity among subjects.

Weight, Body Composition (5 minutes): To assess the BMI and body composition of all subjects, we will perform bioelectrical impedance analysis (BIA). BIA will be conducted with a body fat analyzer (Bodystat 1500, Vacumed, Ventura California) by applying a constant low level alternating electrical current to the individual via electrodes on a scale that subjects step on.

Neuropsychological battery (1 hour): A standardized battery of computerized neuropsychological tests will be administered to measure overall cognitive functioning and change in cognition. We will use three memory tests as primary outcome measures. One is a serial list learning and memory task and the other two are computerized memory and cognition tasks. The entire battery of tests takes approximately 1 hour to complete. Below is a description of each battery.

ModBent
The ModBent is an object recognition task with immediate matching trials and delayed recognition trials. The stimuli used in the ModBent are intersecting sinusoidal curves designed parametrically to be similar to each other in order to evoke the pattern separation cognitive operation. During the immediate matching trials, participants view a single complex stimulus for 10 seconds; following a 1 second delay they are asked to select which one of two objects is identical to the studied stimulus. Following 41 matching trials, participants are shown serially individual complex objects and asked to indicate whether the object is identical to any of the target stimuli studied during the immediate matching trials. There are 82 recognition trials, which include 41 targets and 41 foils. The primary dependent variable for the ModBent is the mean reaction time (ms) for correct rejections of foil stimuli on the delayed recognition trials. Given the previous observation that performance on the Benton Visual Recognition Test (BVRT) is selectively correlated with functioning of the DG and that the putative role of DG in pattern separation, the ModBent was designed specifically to maximize the cognitive operation of pattern separation and tap DG functioning.

NIH Toolbox
According to the NIH Toolbox website: "NIH Toolbox is a multidimensional set of brief measures assessing cognitive, emotional, motor and sensory function from ages 3 to 85, meeting the need for a standard set of measures that can be used as a "common currency" across diverse study designs and settings. NIH Toolbox monitors neurological and behavioral function over time, and measures the domain constructs across developmental stages. This facilitates the study of functional changes across the lifespan, including evaluating intervention and treatment effectiveness."

Neuro-QoL
According to the Neuro-QoL website: "Neuro-QoL is a set of self-report measures that assesses the health-related quality of life (HRQOL) of adults and children with neurological disorders. Neuro-QoL is comprised of item banks and scales that evaluate symptoms, concerns, and issues that are relevant across disorders - along with measures that assess areas most relevant for specific patient populations."

These are all standardized tests commonly used in clinical practice. Gross cognitive function and intelligence measures will be administered at baseline only. All other measures will be given at both testing visits; alternate forms will be used where applicable.

Questionnaire (30 minutes): Food Frequency Questionnaire.

Please attach copies, unless standard instruments are used

Research Related Delay to Treatment

Will research procedures result in a delay to treatment?
No
Treatment to be provided at the end of the study
Not Applicable-Not a Clinical Treatment Study.

Risks/Discomforts/Inconveniences

Risks that could be encountered during the study period

There are no known risks to the optional MRI procedures. Some individuals experience claustrophobia due to confinement of the head in a small space. These subjects will simply discontinue the study. Similarly some might experience back pain from lying on their backs for extended periods of time.

During neuropsychological testing, some subjects might experience some discomfort in performing some of the proposed cognitive tasks in that they might be experienced as too challenging or frustrating.

There are no known risks to cocoa flavanol intake at the intake levels investigated in this study. A recent study[15] reported the following in a trial using diabetic patients:

"No side effects such as headaches, dizziness, skin exanthems, altered bowel habits, bloating, nausea, vomiting, diarrhea, or cardiac adverse events, such as worsening of Canadian Cardiovascular Society or New York Heart Association functional class, myocardial infarction, need for percutaneous coronary intervention and bypass surgery were observed during the entire duration of the trial."[15]
Each subject will be asked for consent to provide a blood sample to confirm menopausal status. Blood will also be drawn for standard medical screening tests. Blood will be drawn by a licensed nurse, doctor or phlebotomist. Risks involve the possibility of experiencing slight pain due to the blood test. There will likely be pain on insertion of the needle into the vein, and there might be slight bruising at the spot where the blood was obtained.

Describe procedures for minimizing risks
To minimize risks during optional MRI procedures, subjects will be screened carefully for contraindications to MRI (e.g., metal implants) and excluded from the study. Similarly, some might experience back pain from lying on their backs for extended periods of time. These individuals will simply discontinue the study.
Following each scanning session, each participant's structural scan is reviewed by a neuroradiologist.
Any issue of medical concern is brought to the participant's attention immediately, and help is offered in obtaining the appropriate referrals to evaluate and potentially treat any medical condition. Similarly, if a participant experiences any psychological distress surrounding scan results, appropriate counseling or referrals will be offered. Dr. Sloan will coordinate the referral process.

To minimize discomfort in some of the proposed cognitive tasks there is careful design and presentation of these that minimize this risk. Subjects have the option of discontinuing participation if their discomfort becomes intolerable. In these rare situations, Dr. Sloan personally meets with the participant to assess potential functional implications of the test results. Based on this assessment, a decision is made about whether to suggest further clinical evaluation and appropriate referrals are offered.

We will take every precaution to minimize discomfort when obtaining blood. If there is any difficulty in obtaining the blood or if there is some medical reason why the subject cannot allow us to perform the blood test, the subject will simply discontinue the study.

Methods to Protect Confidentiality

Describe methods to protect confidentiality

In the informed consent form, subjects are told that the information they provide and all findings will be kept strictly confidential, with access limited to the research staff and the possible exception of state or federal regulatory personnel. No one but designated project staff will have access to the master list linking subjects' names to code numbers, and all information obtained will be coded. Data will be analyzed without reference to personal identifying information, and this information will be carefully protected within the database. All paper files will be kept in locked file cabinets.

Optional MRI sub-study
MRI results (including scan images and accompanying data) will be stored in the Program for Imaging and Cognitive Sciences database at the Columbia University Medical Center and accessible only to the members of the research team. MRI reports (including the results of the clinical reading) will be de-identified and stored in a locked file cabinet in the office of Dr. Richard Sloan, Director of the Behavioral Medicine Program at the Columbia University Medical Center.

Will the study be conducted under a certificate of confidentiality?
No

Direct Benefits to Subjects

Direct Benefits to Subjects
Subjects will not directly benefit from participating in the study.

Compensation and/or Reimbursement

Will compensation or reimbursement for expenses be offered to subjects?
Yes
Please describe and indicate total amount and schedule of payment(s).
Include justification for compensation amounts and indicate if there are bonus payments.

Compensation and Travel Reimbursement
Subjects will be paid $40 for each of the five neuropsychological testing sessions for a total of $200. If subjects are 90% adherent to capsule consumption and complete all evaluations at the end of the study, subjects will receive $50 bonus for a possible total of $250.

If subjects agree to participate in the MRI sub-study, they will be paid $70 for each of the two MRI scans. If subjects are 90% adherent to capsule consumption and complete all evaluations at the end of the study, subjects will receive $60 bonus for a possible total of $200.

Subjects will also receive travel reimbursement of $10 for each evaluation visit.

Payment Card Program

We are participating in the pilot phase of the Payment Card Program directed by the Global Treasury Operations at Columbia University. Subjects will be compensated through a debit card provided for them by our research team. The debit cards are issued by Bank of America (BOA).

In order to register subjects to their debit cards, subject's name, address, and phone number will be provided to BOA. Subjects will receive one reloadable card and the card will be "reloaded" within 2 weeks after each completed study visit. This card can be used as a credit card OR as an ATM card. Subjects would also be able withdraw money from a bank either through a bank teller or an ATM machine.

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Uploads

Upload the entire grant application(s)
Upload copy(ies) of unbolded Consent Form(s)
Upload copy(ies) of bolded Consent Form(s)
Upload copy(ies) of the HIPAA form
HIPAA Form A.pdf
HIPAA NYSPI Form.pdf
Upload any additional documents that may be related to this study

HIPAA Form A

HIPAA Clinical Research Authorization for Sponsored Research

Protocol Number: 7034
Name of Study: Dietary Cocoa Flavanols and Age-Related Memory Decline
Principal Investigator: Dr. Richard P. Sloan

For the purpose of the conduct of the above name study, I agree to permit Columbia University Medical Center, my doctors and my other health care providers (together "providers"), and Dr. Richard P. Sloan and his/her staff (together "Researchers"), to use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
   - all information collected during the research described in the Informed Consent Form for the above-named study ("the research"); and
   - health information in my medical records that is relevant to the Research.
   - This may include medical history information that may be considered sensitive, including:

2. **The providers may disclose health information in my medical records to:**
   - the Researchers;
   - the sponsor of the Research, Mars Inc., and its agents and contractors (together "Sponsors") and;
   - representatives of government agencies, review boards, and other persons who watch over the n safety, effectiveness, and conduct of the research.

3. **The researchers may use and share my health information:**
   - among themselves and with other participating researchers to conduct the Research;
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - as permitted by the Informed Consent Form.

4. **The Sponsor may use and share my health information as permitted by the Informed Consent Form.**

5. **Once my health information has been disclosed to a third party (e.g., a pharmaceutical company participating in this Study), federal privacy laws may no longer protect it from further disclosure.**

6. **Please note that:**
   - You do not have to sign this Authorization, but if you do not, you may not participate in the Research.
   - You may change your mind and revoke (take back) this authorization at any time and for any reason. To revoke this Authorization, you must write to:

Dr. Richard P. Sloan
Behavioral Medicine Program,
Dept. of Psychiatry Columbia University Medical Center
622 West 168th Street, Suite 1540

. However, if you revoke this Authorization you will not be allowed to continue part in the Research. Also, even if you revoke this Authorization, the Researchers and the Sponsor may continue to use and disclose the information they have already collected as permitted by the Informed Consent Form

. While the Research is in progress, you may not be allowed to see your health information that is created or collected by Columbia University in the course of the Research. After the Research is finished, however, you may be allowed to see this information.

7. This Authorization does not have an expiration (ending) date.

8. You will be given a copy of this Authorization after you have signed it.

Printed Name of Subject: _____

Signature of Subject or Legal Representative: _____ Date: _____

Relationship of Legal Representative to Subject (if applicable): _____

New York State Psychiatric Institute (NYSPI)
Authorization to Use or Disclose Health Information during a Research Study

Protocol Number: 7034 **Principal Investigator:** Dr. Richard P. Sloan, Ph.D.

Name of Study: Dietary Cocoa Flavanols and Age-Related Memory Decline

Before researchers can use or share any identifiable health information ("Health Information") about you as part of the above study (the "Research"), the New York State Psychiatric Institute (NYSPI) is required to obtain your authorization. You agree to allow the following individuals and entities to use and disclose Health Information about you as described below:

- New York State Psychiatric Institute (NYSPI), your doctors and other health care providers, if any, and
- The Principal Investigator and his/her staff (together "Researchers"). Researchers may include staff of NYSPI, the New York State Office of Mental Health (OMH), Research Foundation for Mental Hygiene, Inc. (RFMH), and Columbia University (CU), provided such staff is a part of the study, and
- Providers of services for the Research at CU, NYSPI and/or RFMH, such as MRI or PET, or Central Reference Laboratories (NKI), if indicated in the consent form.

1. **The Health Information that may be used and/or disclosed for this Research includes:**

☑ All information collected during the Research as told to you in the Informed Consent Form.
☑ Health Information in your clinical research record which includes the results of physical exams, medical and psychiatric history, laboratory or diagnostic tests, or Health Information relating to a particular condition that is related to the Research.
☐ Additional information may include:

2. **The Health Information listed above may be disclosed to:**

☑ Researchers and their staff at the following organizations involved with this Research:
Columbia University Medical Center

☐ The Sponsor of the Research,

and its agents and contractors (together, "Sponsor"); and
☑ Representatives of regulatory and government agencies, institutional review boards, representatives of the Researchers and their institutions to the level needed to carry out their responsibilities related to the conduct of the research.
☐ Private laboratories and other persons and organizations that analyze your health information in connection with this study

☐ Other (family members or significant others, study buddies, outside agencies etc.) Specify:

3. By giving permission to release your Health Information as described above, you understand that your Health Information may be disclosed to individuals or entities which are not required to comply with the federal and state privacy laws which govern the use and disclosure of personal Health Information by NYSPI. This means that once your Health

Information has been disclosed to a third party which does not have to follow these laws (e.g., a drug company or the Sponsor of the Research), it may no longer be protected under the HIPAA or NYS Mental Hygiene Law requirements but is subject to the terms of the consent form and may be subject to other state or federal privacy laws or regulations.

4. **Please note that:**
   - You do not have to sign this Authorization form, but if you do not, you may not be able to participate in the study or receive study related care. You may change your mind at any time and for any reason. If you do so, you may no longer be allowed to participate in the study. If you withdraw this Authorization the research staff and the Sponsor, if this is sponsored research, may still use or disclose Health Information containing identifying information they already have collected about you as needed to maintain the reliability of the research. Any request to withdraw this Authorization must be made in writing to (enter name and contact information below):

     Dr. Richard Sloan, Ph.D. 622 West 168th Street, PH Suite 1540, New York, NY 10032
     Tel: 646-774-8940 Email: rps7@cumc.columbia.edu
   - While the Research is going on, you may not be allowed to review the Health Information in your clinical research record that has been created or collected by NYSPI. When this research has been completed you may be allowed to see this information. If it is needed for your care, your Health Information will be given to you or your Doctor.

5. **This Authorization does not have an end date.**

6. **You will be given a copy of this form after you have signed it.**

I agree to the use and disclosure of Health Information about me as described above:

_____ _____

Signature of Participant/ Legal Representative Date

_____

Printed Name of Participant

_____

Relationship of Legal Representative to Participant (if applicable)

We also ask you or your legal representative to initial the statements below:

☐ **I have received a copy of the NYSPI/OMH Notice of Privacy Practices.**