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COSMOS-Mind PROTOCOL

1. BACKGROUND

This study will be conducted in partnership with a large funded randomized controlled trial, the **CO**coa **S**upplement and **M**ultivitamin **O**utcomes **S**tudy (COSMOS),[1,2] and will examine the potential cognition-protecting effects of high-potency cocoa flavanol extract, with and without co-administration of a standard multivitamin (MTV) in adults 65 years and older, concurrently with their evaluation of cardiovascular disease (CVD) and cancer endpoints.

Cocoa Flavanol Effects on Cardiovascular Health

Cocoa, in its unprocessed form, contains high quantities of catechins and epicatechins, a subclass of flavonoids known as flavanols,[3,4] and theobromine, an alkaloid of the cacao bean with vasodilation properties.[5] Although the benefits of flavonoids have been studied for years, the health-promoting effects of cocoa flavanols caught the attention of the scientific community and public when low rates of hypertension and mortality due to CVD were reported in Kuna Indians living in the remote San Blas islands off the coast of Panama – protections that were lost with migration to urban areas. Extensive studies of the Kunas' lifestyle identified their dietary exposure to large amounts of cocoa flavanols as the primary contributing factor.[6] Observational studies consistently demonstrate an inverse association between cocoa flavanol consumption and risk of CVD,[7-10] and in clinical trials cocoa flavanols have robust favorable effects on cardiovascular health,[11-15] influencing endothelial function and flow-mediated dilation,[16,17] blood pressure,[18-20] platelet adhesion and aggregation,[21,22] lipid profiles,[20,23,24] antioxidant capacity,[20,25,26] systemic inflammation,[27] and insulin sensitivity and β-cell function.[20,28,29] Pilot trials of up to 100 participants with 4-12 weeks of varying doses of cocoa flavanols in different patient groups provide consistent evidence for cardiovascular benefits at doses >700 mg/day and without adverse events.[20,29-33] However, the benefits of cocoa flavanols on clinical CVD events in older adults have yet to be examined in a definitive trial.

Cocoa Flavanol Effects on Cognition and Brain Function

COSMOS-Mind will examine whether cocoa flavanols protect and even enhance cognitive function in older adults, an appropriate extension of the parent trial given the robust association between vascular and cognitive health.[34-36] This association was the focus of a recent study of over 9,000 older adults drawn from the National Alzheimer's Coordinating Center: increased vascular risk, which included history of CVD and atrial fibrillation, predicted faster rates of cognitive decline in cognitively normal adults and in individuals with mild cognitive impairment (MCI).[36] Dietary consumption of cocoa flavanols may slow this decline through its beneficial effects on cerebral vasodilation, and thus on brain blood flow and perfusion, and angiogenesis.[37,38] Epicatechin, the most common flavanol in cocoa, is rapidly absorbed, readily crosses the blood-brain barrier, can be detected in the brain,[39-41] and likely has accumulating physiological effects at high doses.[40,42] This evidence for brain penetrance provides an important foundation for other cognition-enhancing mechanisms of flavanols at the neuronal level.[43,44]

The effects of cocoa flavanols on cognition have been examined in animal studies for years, and consequently, putative underlying mechanisms related to endothelial function and pivotal signaling cascades for neuronal activity and viability are well described.[38] However, these mechanisms have not been fully explored in controlled clinical studies. Much of the support for a cognition-enhancing effect of flavanols in healthy older adults comes from observational studies, and a few small but promising controlled trials.[45,46] In one large prospective study of 1640 older adults (≥65 yrs) followed for 10 years,[47] dietary intake of flavonoid-rich food (dark chocolate, wine, tea) was positively correlated with cognitive performance at baseline and over time in a dose-dependent manner. At the end of follow-up, participants in the lowest quartile for flavonoid

intake had lower Mini-Mental State Examination (MMSE) scores vs. those in the highest quartile. A favorable dose response of flavonoid intake on cognition was also reported in a large cross-sectional Norwegian study for a more extensive set of outcomes measuring attention and task-switching, verbal fluency, and spatial perception.[45] Regular flavonoid intake has also been linked to lower rates of prevalent cognitive impairment[48] and incident dementia.[49,50]

Only a handful of controlled trials have examined the potential benefits of regular cocoa flavanol intake on cognitive function in older adults. While a few studies have failed to show cognitive benefits of cocoa flavanols,[37,51-53] others provide compelling support to suggest that regular use of the high potency form of the extract may protect and possibly enhance cognitive function,[20,54,55] a variability that likely reflects differences in methodology and/or extract formulation. In a small randomized, double-blind, 3-month trial of a high potency cocoa flavanol extract that is very similar to that administered in COSMOS, Brickman, et al. reported increased blood flow in the dentate gyrus and an associated improvement on a validated dentate gyrus-dependent memory task in older adults (50-69 years).[54] The strongest support for the proposed study is provided by the results of the Cocoa, Cognition, and Aging Study, a double-blind, 8-week randomized controlled trial of cocoa flavanols in 90 cognitively healthy older adults[20] and in 90 individuals with amnestic mild cognitive impairment (MCI)[55] at high risk for AD dementia. Participants consumed a daily drink with a high (993 mg) or medium (520 mg) dose, versus a low (45 mg) dose, of cocoa flavanols. Compliance exceeded 97% without adverse events. In both the healthy and MCI cohorts, performance on tests of attention and processing speed, task-switching and working memory, verbal fluency, and the global cognitive composite outcome improved for those in the high- and medium-dose groups relative to the low-dose group. In these participants, cocoa flavanols also lowered systolic and diastolic blood pressures, increased insulin sensitivity, and reduced a potent marker of oxidative stress. In both groups, a favorable treatment effect on insulin sensitivity was the primary determinant of cognitive response, consistent with a substantial body of work linking glucose regulation and cognitive function in older adults.[56-59] This insulin sensitizing effect of cocoa flavanols, also reported by others,[13] has important implications for older adults for whom the combined prevalence rate of type 2 diabetes and prediabetes exceeds 75% nationwide.[60] These findings demonstrate the potential efficacy of cocoa flavanol supplementation in the dose range proposed, and set the stage for this trial in cognitively healthy and mildly impaired older adults that will test whether regular intake of high dose cocoa flavanols can protect cognitive function and thus slow cognitive decline associated with normal and pathological aging, including AD. The extract's excellent tolerability profile provides added translational value.

Micronutrient Supplementation (Multivitamin) Effects on Cognition

COSMOS-Mind will also test whether daily use of a standard multivitamin benefits cognition in older adults. Although essential nutrient deficiencies in older adults have been associated with a higher risk of cognitive decline and dementia,[61] the results of other studies examining MTV use for cognitive benefit remain controversial.[62] Multivitamin use alone or with other therapies to enhance cognitive function in older adults has not been adequately examined in large randomized controlled trials (RCTs).[63] Controlled trials of a single nutrient focused on folic acid with or without other B vitamins,[64,65] omega-3 fatty acids,[66,67] and vitamin D[61,68,69] have yielded mixed results, which could reflect the absence of a cognitive benefit or limitations in study design. Some of the design issues that contribute to this variability relate to the specific micronutrients administered and their interactions with one another, the cognitive tests selected, and variability in participant demographics and nutritional status.[63,70] In the population-based Canadian Study of Health and Aging examining dementia onset in adults aged 65 years and older, participants reporting regular use of MTVs at baseline were less likely to experience significant cognitive decline during the 5-year follow-up.[71] In a large RCT recruiting from multiple health care facilities in Scotland, daily use of a balanced multivitamin for 1 year improved verbal fluency, but only for those at least 75 years old or with a possible micronutrient deficiency at baseline (as per a risk questionnaire).[72] The Physician's Health Study (N=5947, ≥65 years old) reported no effect of multivitamin use on cognition in older men.[73] These studies raise the possibility that micronutrient supplementation may only benefit cognitive function in adults who are vulnerable due to advanced age or poor nutrition. However, the effects of MTVs on cognition in older women have not been adequately examined in a large RCT.

2. OBJECTIVES

COSMOS-Mind is an ancillary cognitive study to the large randomized double-blind, placebo-controlled COSMOS trial, coordinated through Brigham and Women's Hospital (BWH). The parent trial will test whether high-potency cocoa extract supplement administered alone or in combination with a standard multivitamin reduce risks of CVD and cancer in older adults. COSMOS-Mind will test whether 3 years of treatment with these supplements improves cognitive function and reduces risk of cognitive impairment, including AD and other forms of dementia.

Primary Aim

- Test whether random assignment to daily cocoa extract (capsule containing 750 mg/d flavanols, including 75 mg (-)-epicatechin, and 90 mg theobromine), compared to placebo, has favorable effects on a composite measure of cognitive function, over 3 years of follow-up in men and women who are 65 years and older

Secondary Aims

- Examine the effects of MTV use over 3 years of follow-up, relative to placebo, on a composite measure of cognitive function
- Assess treatment effects on incident MCI, and AD and other related dementias
- Compare intervention effects on cognitive domains of executive function and episodic memory

Tertiary Aims

- Examine consistency of treatment response for subgroups defined by age, sex, body mass index, baseline cognitive status, CVD, and type 2 diabetes
- Examine treatment effects on measures of sleep quality, depressive symptoms, and subjective memory concerns
- Share COSMOS-Mind data with the parent trial and its ancillary studies to expand its scientific impact

3. DESCRIPTION OF PARENT TRIAL (COSMOS)

COSMOS is supported through an investigator-initiated award from Mars SymbioScience (PIs: Drs. Manson and Sesso of BWH), and is a randomized, double-blind, placebo-controlled, 2x2 factorial clinical trial in 18,000 older women and men. The trial is testing a patented, well-studied cocoa extract supplement (capsules containing 750 mg/d flavanols, including 75 mg (-)-epicatechin, and 90 mg theobromine) and a daily MTV (Centrum Silver®, provided by Pfizer) in the prevention of CVD and cancer. COSMOS participants will be recruited from 2 large national cohorts of older adults (Women's Health Initiative Extension Study [observational; N=73,991]; VITamin D and OmegA-3 TriaL [eligible but unenrolled candidates; N=89,373]). The mean treatment and follow-up period in COSMOS will be 4 years. Participants will be asked to forego personal use of MTV and cocoa extract supplements while in the trial. Adherence and dietary intake of non-study supplements will be assessed via self-report using semi-annual questionnaires and pill count with nutrient biomarker measurements in a subset. A 3-month placebo run-in will eliminate those with poor compliance before randomization.

4. STUDY POPULATION

Inclusion and Exclusion Criteria

COSMOS-Mind will **include** 2500 participants from the parent trial who are at least 65 years of age, with approximately equal distribution of women and men.

The study will **exclude** participants with insulin-dependent diabetes. Insulin therapy, often associated with chronic hyperinsulinemia, can worsen cognition[74] and therefore potentially mask beneficial effects of the cocoa flavanols. COSMOS participants co-enrolled in the WHI Memory Study (WHIMS) will be excluded given their prior exposure to COSMOS-Mind cognitive tests. Also, participants who are unable to complete the baseline cognitive assessment will not be permitted to continue in the study. Adults with dementia will likely self-select out of enrollment in COSMOS-Mind, or be excluded given the demands of the placebo run-in period required for COSMOS. For the few with mild dementia who may enroll in COSMOS-Mind, randomization will ensure equal distribution by treatment assignment. Pre-enrollment cognitive assessments to identify dementia are not feasible for this large simple trial.

Recruitment and Consenting

Eligible COSMOS participants will be approached for enrollment in COSMOS-Mind and a second cognitive ancillary study ("COSMOS-Web": involves a brief online computer assessment) using a single approach letter and recruitment flyer during the placebo run-in phase of the COSMOS trial. These materials provide information about COSMOS-Mind, expectations of participants, what is provided to participants, and how to enroll in the sub-study. Participants can choose to participate in one, both, or neither sub-study and will let the BWH Coordinating Center know of their decision by completing and returning a provided form. Consent to participate will be implied when participants indicate their willingness to participate in COSMOS-Mind on this form or by informing the COSMOS team by telephone or email. Implied consent will be used given the low participant burden and low risk associated with study participation as per Wake Forest School of Medicine IRB accepted practices.

Once enrolled, the COSMOS team at BWH will provide contact information and other parent trial outcomes for COSMOS-Mind participants to the Wake Forest COSMOS-Mind team using a secure web-based data transfer system. This seamless exchange of information between sites will permit timely accounting to ensure that the targeted demographics for enrollment are achieved (e.g. gender, age, race, ethnicity).

5. OUTCOMES

Face-to-face assessments of cognitive functioning are expensive in large multi-site studies and thus telephone-based protocols have been developed and validated. Telephone-based assessments have been used successfully in other studies and provide a valid and cost-effective method for tracking changes in cognitive status, including the development of MCI and dementia.

COSMOS-Mind will administer a telephone cognitive assessment to all participants annually by trained and certified staff of the Wake Forest COSMOS-Mind team. On the initial COSMOS-Mind call, consent to participate in the study will be confirmed and a brief hearing test will be administered to assess the participant's ability to successfully complete the interview. The interview will be 45 to 60 minutes in duration, and will include social time to support the relationship, and time to complete the hearing screening, cognitive tests, and questionnaires. The assessment battery consists of 6 validated tests and 3 validated questionnaires. A fourth validated questionnaire may be administered to a knowledgeable friend or family member (informant) identified by the participant if cognitive scores fall below pre-specified thresholds on a test of global cognition (i.e., TICSm) at any assessment.

A secure web-based call tracking system will be used to monitor participant contact, assessment dates, and attempts to complete interviews. Standard administration procedures of the telephone cognitive assessment will be for examiners to first record participants' responses on paper versions of the tests and then at a later time, enter the data into a dedicated and secure web-based database management system. As a quality assurance measure, each administration of the cognitive battery will be electronically audio-recorded to assist the examiner in scoring and to allow data quality assurance checks. Examiners will be trained and certified before administering their first assessment to a participant. Annual re-certification will be required.

Hearing Assessment

Before administration of the cognitive test battery, each participant will be asked a set of standardized questions: “Do you usually have trouble hearing when one person speaks to you?” “Do you usually have trouble hearing over the phone?” “Can you hear me well enough?” “Do you use a hearing device?” and “Is it in place?” and asked to repeat, “I have a cat so all I need is a dog.” Based on the participant’s responses, the examiner will adjust his/her test administration as needed. If hearing acuity is deemed significantly impaired, the examiner will terminate the assessment and the participant will not be permitted to continue in the study.

Cognitive Assessment

Telephone Interview for Cognitive Status-modified (TICSm) measures global cognitive function.[75] Fourteen items assess orientation, attention, language, learning and memory, psychomotor skills and abstraction. A modification to the original TICS added a second free recall trial to assess delayed memory for the 10-item word list.[76] In COSMOS-Mind, a third recall trial will be administered 15 minutes after this second recall trial, to quantify long delayed memory for the list. The TICSm has been previously validated for administration in older adults[75-79] and used in large-scale epidemiological studies of cognitive impairment.[80] The TICSm correlates highly with other measures of global cognitive function, including the Mini-Mental State Exam (r=0.86), the Clinical Dementia Rating scale (r=-0.75), and with comparable cognitive tests administered face-to-face.[79,81-83] The TICSm has excellent sensitivity (0.87) and specificity (0.89) to differentiate older persons with and without dementia[84] and to identify amnestic MCI,[85] and scores are normally distributed in population studies.[86]

Immediate and Delayed Story Recall (SRI & II) measures verbal memory.[87] Participants are read a short story of 25 distinct elements, and are asked to recall as many elements as possible immediately after hearing the story (SRI) and again 15-20 minutes later (SRII). Alternate parallel forms of Story Recall will be administered from one annual assessment to the next, in counterbalanced order across participants, to minimize practice effects.

Oral Trail Making Test (OTMT)[88,89] is a modified version of the original Trail-Making Test (TMT)[90] that measures attention (Part A) and executive function (Part B). The OTMT is highly correlated with the original TMT.[91] For Part A, participants are asked to count from 1 to 25 as quickly as possible. For Part B, participants recite numbers and letters in an alternating fashion (1-A-2-B-3-C…13) as quickly as possible. Time to complete each task (seconds) is recorded.

Verbal Fluency is a measure of language accessibility and will be assessed using two tasks. *Category Fluency* requires participants to name as many exemplars of a semantic category as possible in 1 minute; two trials will be administered (categories = animals, vegetables). *Letter Fluency* requires participants to name as many words that begin with a specific letter of the alphabet in 1 minute; two trials will be administered (letters = F, L).[92]

Number Span Test (NST)[93] measures simple attention and working memory (i.e., ability to manipulate transitory information in short-term memory). This task requires the participant to repeat a series of single-digit numbers of increasing span length, first in the same order as presented by the examiner (*Number Span Forward*) and subsequently in the reverse order (*Number Span Backward*). Number of correct responses is recorded.

Digit Ordering Test (DOT)[93] is a task of working memory. Participants are read a series of single numerical digits and are asked to recite the numbers in order from lowest to highest (e.g., ‘2-7-1’ would be reordered as ‘1-2-7’). For each span length, 2 trials are administered. Span is increased by 1 number until participants are unable to successfully complete both trials of a given span length. Number of correct responses is recorded.

Additional Measures

Cognitive Change Index (CCI)[94] is a self-report questionnaire listing common experiences (e.g., "recalling conversations a few days later", "remembering names and faces of new people") and participants indicate amount of perceived change over a specified duration in the past (e.g., 5 years) using a Likert scale. To reduce participant burden, only the first 12 questions that address subjective memory concerns will be used to calculate the CCI score. The same 12-item subscale is used in the large multicenter Alzheimer's Disease Neuroimaging Initiative-2 study.

Geriatric Depression Scale-Short Form (GDS-SF) measures depressive symptom severity,[95,96] which is known to affect cognitive function. This 15-item (Yes/No) questionnaire can be administered orally, and has excellent psychometric properties and normative data.[97,98] Participants who score >8 on this scale or whose general responses to examiners' questions suggest significant emotional distress will also receive the supplemental Emotional Distress Test, which includes standardized questions about depressive severity and suicidal ideation. If a participant indicates any suicidal inclination, a study clinician experienced in the assessment and treatment of geriatric psychiatric disorders (Dr. Rapp) will be informed, and will contact the participant to evaluate risk and make recommendations for follow-up.

Women's Health Initiative Insomnia Rating Scale measures sleep disturbance and insomnia, which are known to impact cognitive function. This 5-item self-report questionnaire has excellent reliability and construct validity, and is sensitive to change over time.[99,100]

Adjudication of Cognitive Status to Identify MCI, AD and Other Dementias

COSMOS-Mind will use the same procedures for ascertaining MCI and probable dementia (including AD) that were developed for WHIMS. All participants will be asked to identify a reliable informant at the time of the first telephone contact who could provide information about the participant's cognitive and functional status. After each telephone cognitive assessment, suspected cases of cognitive impairment will be identified when TICSm<31, or, in follow-up Years 1-3 when the TICSm score drops by 0.5 of a standard deviation relative to age-appropriate normative data. For these participants, a trained interviewer will contact their informant to conduct a structured interview to complete the Dementia Questionnaire (DQ). This interview includes questions about current cognitive and behavioral functioning, and medical events and conditions that could impact cognition (e.g., stroke, psychiatric disorders).

In Years 4 and 5, after the planned follow-up annual evaluations are completed, all available test results and medical information for participants who triggered a DQ at any time during the study will be provided to 2 independent dementia experts. The information reviewed will include: cognitive data; self-report questionnaires about cognitive concerns, depression, sleep disturbances, and information on hospitalizations, medications and disabilities; informant responses on the DQ; and relevant health information available through the parent trial (including cardiovascular events and cancers). MCI classifications will include amnestic single domain, amnestic multi-domain, non-amnestic single domain, or non-amnestic multi-domain. If the adjudicator dyad agrees on the primary classification (MCI, probable dementia), no further discussion will occur; if the dyad disagrees, the case will be discussed by the entire adjudication panel until consensus is reached. Disagreements regarding MCI sub-classifications will be resolved within dyads and, if not possible, by the entire adjudication panel. For participants who receive a classification of 'dementia,' a letter will be sent to notify them that the test results indicated a possible cognitive impairment, and to encourage follow-up with a physician and further evaluation.

6. STATISTICAL CONSIDERATIONS

The primary outcome for COSMOS-Mind is a composite measure of cognitive function that combines individual assessments of global cognitive function (TICSm), memory (SR), and executive function (OTMT, Verbal Fluency, NST, DOT). The composite provides a quantifiable measure of cognitive function across multiple domains and greater statistical power than individual measures even if the intervention effect varies moderately from one individual measure to another. It consolidates type 1 error into a single outcome. Secondary analyses, described below, will examine intervention effects on the constituent measures of the composite score.

The primary hypothesis is that random assignment to high potency cocoa flavanol extract compared to placebo will result in a mean difference over time in the global cognitive composite score. This hypothesis will be tested using 2-tailed type 1 error of 0.05. Inference will be based on the marginal effect estimated from a factorial study design, and a generalized linear model[101] with the dependent variable consisting of all measured annual changes from baseline across years of follow-up on every participant, regardless of adherence (i.e. intent-to-treat). Data from the individual tests will be combined using a multivariate analysis of covariance (MANOVA) model within this framework with adjustment for sex, education, and age. In this model, all observed data can be included without special procedures for missing data, provided they are missing at random. The estimated differences will be combined using the ordinary least squares global test statistic.[102,103] This statistic is the sum of the estimated differences of the individual tests divided by their standard errors, which produces a test statistic that is approximately normal with mean zero under the null hypothesis of no difference. Its standard error will be computed from the estimated correlation matrix of the treatment group differences. Cocoa flavanol effects will be examined by comparing cognitive response to active cocoa extract vs. its placebo, regardless of assignment to active MTV or its placebo.

Secondary and tertiary aims. COSMOS-Mind will assess the relative effects of assignment to MTV using parallel analyses to those described above. The study will also assess whether effects of the two treatments interact on the primary outcome, adding a term to the model used in the primary hypothesis. If so, results from the primary marginal comparisons will be qualified. Individual cognitive test scores will be analyzed – paralleling the strategy used to test the primary hypothesis – in supporting analyses. The randomization effects on tertiary outcomes including cognitive complaints, sleep quality, and depressive symptoms will be assessed similarly to the intervention models used in the primary and secondary aims, and further tests will determine whether the treatments interact with respect to tertiary outcomes. Linear contrasts will be used to estimate treatment effects at 3 years. Tests of interactions will also assess the potential moderating effect of treatments among subgroups formed by age (<70 or $\geq$70 years old), sex, BMI (<25, 25-29, $\geq$30 kg/m^2), baseline cognitive function (median split on TICSm), cognitive complaints (median split on CCI), depressive symptoms (median split on GDS-SF), hypertension, and diabetes; additionally, the preceding variables will also be assessed as continuous moderators of the intervention effects. The distribution of follow-up times to MCI and dementia will be assessed with proportional hazards regression. COSMOS-Mind will incorporate CVD and cancer events (from the parent trial) as change-points in the primary analyses to assess their impact on post-event cognitive trajectories. When needed, transformations (e.g. Box-Cox, rank, probit) will be used to improve the symmetry of residual distributions.

Interim Testing

No interim monitoring of treatment effects on cognitive outcomes is planned. COSMOS-Mind investigators will remain masked to treatment assignment until the parent trial is completed. Routine reports will assess retention, data completeness and quality, and cognitive trajectories over time. These reports will be sent to the COSMOS Coordinating Center for inclusion in DSMB reports.

Statistical Power

Longitudinal sequences of cognitive test scores from the WHIMS-ECHO study (N=2,878; 1-6 years of annual telephone assessments) were used to calculate the longitudinal covariance of measures in a simulation analysis. Loss-to-follow-up was set to accumulate at 5% per year, as per rates observed in WHIMS.[104] Based

on previous studies,[20,55] the intervention effect appears quickly and is sustained over time. Calculations are based on 2-sided tests with type 1 error set to 0.05 and 90% power for the primary outcome of a composite across all cognitive tests. Based on these and other projections, the 2500-person sample in COSMOS-Mind will provide >90% power to detect a sustained effect size of 0.10 SD and a waning effect size that initially is 0.15 SD; it also provides some leeway should the assumptions made above be not fully realized. Limiting follow-up to 3 years allows a more extended enrollment and analysis period, and reduces the number of assessments.

7. CONFIDENTIALITY

Appropriate measures will be in place to protect against risk of disclosing confidential information. The data will be collected for research purposes only. All paper records of the telephone assessments will be stored in locked cabinets in locked rooms, accessible only to the COSMOS-Mind investigators and staff. Participants will be assigned a unique study identifier code on all study questionnaires and forms. All electronic data – including the master list pairing participants' names and codes, recordings of telephone assessments, personal health information, and study outcomes – will be stored in password-protected files on a secure network in a secured area. This network is protected with frequently-updated anti-virus and anti-Trojan software, limited file sharing and file permissions to approved users only, and automated monitoring of access attempts; these procedures have successfully maintained security for many multicenter clinical trials coordinated by Wake Forest. COSMOS-Mind and COSMOS will develop data transfer procedures and protocols using password protection and encryption, to permit seamless and secure exchange of information. Safety monitoring will be provided by the DSMB of the parent trial.

8. SAFETY MANAGEMENT

Potential Risks

The COSMOS-Mind procedures pose minimal risk to participants, which are primarily related to possible emotional discomfort related to cognitive testing and answering questions relating to self-perceptions of memory and mood. Participants could experience distress when learning that they may have a significant cognitive impairment, following adjudication by dementia experts. COSMOS-Mind will only be contacting those with suspected dementia (i.e. not those with MCI), thus the letter will likely support preexisting suspicions regarding the participant's cognitive status.

Cognitive and Mood Assessment

Examiners will be extensively trained to identify and appropriately respond to discomfort associated with cognitive testing, or questions about self-perceptions of memory or mood, including discontinuing the assessment, if necessary. A study clinician experienced in the assessment and treatment of geriatric psychiatric disorders (Rapp) will contact participants who express suicidal ideation in the context of the mood assessment. Similar telephone-based testing protocols have been extensively used in other studies (e.g., WHIMS-ECHO, WHIMS-Y) with relatively fewer reports of participant discomfort in telephone-based versus face-to-face assessments.

Disclosure Regarding Suspected Cognitive Impairment

Participants with an adjudicated classification of probable dementia will receive a letter to alert them that the COSMOS-Mind test results suggest a significant cognitive impairment and to advise them to follow-up with their personal physician. A Release of Information form will be included with the letter with instructions to sign and return this form to the COSMOS-Mind team to request a summary of the results be sent to his/her primary care provider. The adjudication panel of dementia experts (Baker, Rapp, Sachs) will be available to these

participants by telephone upon request. This disclosure protocol, developed for WHIMS has identified over 400 cases of probable dementia since WHIMS was initiated.

A 'Cognitive Alert' will be generated when an informant endorses items on the DQ that indicate impaired functional status (i.e.: 'yes' to any of Q1-Q6 ~AND~ 'yes' to any of Q14-16, Q18; ~OR~ answer to Q10 indicates diagnosis of dementia or AD). When this occurs, members of the adjudication team (Baker, Rapp) will review the available test results to assess whether a classification of dementia is warranted. If so, the participant will receive the alert letter informing them of a possible cognitive impairment and to encourage follow-up.

Protection against Risk

The principles listed in the current edition of the Declaration of Helsinki will be implemented. Appropriate measures will be in place to protect against the risk of disclosing confidential information. The data will be collected for research purposes only. All paper records of the telephone assessment will be stored in locked cabinets in locked rooms, accessible only to the COSMOS-Mind investigators and staff. Participants will be assigned a unique study identifier code on all study questionnaires and forms. All electronic data – including the master list pairing participants' names and codes, recordings of telephone assessments, personal health information, and study outcomes – will be stored in password-protected files on a secure network in a secured area. This network is protected with frequently updated anti-virus and anti-Trojan software, limited file sharing and file permissions to approved users only, and automated monitoring of access attempts. These procedures have successfully maintained security for many multicenter clinical trials. COSMOS-Mind will work with the COSMOS team at BWH to develop data transfer procedures and protocols using password protection and encryption, to permit seamless and secure exchange of information. Safety monitoring will be provided by the DSMB of the parent trial.

Potential Benefits of the Proposed Research to Human Subjects and Others

There is an urgent need to identify effective strategies to slow or prevent age-related cognitive decline. Although there may be no direct benefit to the participant for taking part in the study, COSMOS-Mind will provide a time- and cost-efficient assessment of whether a promising, safe, and widely translatable intervention can preserve cognitive function in older adults.

Importance of the Knowledge to be Gained

COSMOS-Mind will expand the scientific scope of the parent trial to include data about potential cognitive effects of the treatments that may reduce risk of cardiovascular disease and cancer in older adults. This intervention is inexpensive, easily accessible, and safe. If daily use of high-potency cocoa flavanol extract, with or without a multivitamin, attenuate age-related cognitive decline and impairment, this research could have significant implications for standard of care to protect and preserve cognitive function in a fast-growing aging population in the US and worldwide.

Data and Safety Monitoring Plan

As an ancillary study to COSMOS, COSMOS-Mind will adhere to the reporting procedures to be established by the COSMOS DSMB. The COSMOS DSMB is expected to include representatives from the established VITAL and WHI DSMBs, together with additional experts in epidemiology, biostatistics, and other relevant clinical areas, including CVD and cancer. The possibility that an adverse event is reported during the telephone assessment is small; however, should this occur, staff will notify the COSMOS team to initiate their safety protocols.

9. REFERENCES

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