PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Olivia I. Okereke, MD, SM

PROTOCOL TITLE

VITAL-DEP: Depression Endpoint Prevention in the VITamin D and OmegA-3 TriaL

FUNDING

1 R01 MH091448-01A1 from the National Institutes of Health (NIH)

VERSION DATE

March 27, 2012

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Our aim is to investigate prospectively the effect of two agents – vitamin D and omega-3 fatty acids – for reducing the risk of depression and yielding better mood scores in the context of a large randomized clinical trial with 5 years of follow-up. Specifically, the ***VIT***amin D and Omeg***A***-3 Tria***L*** (***VITAL***) was just funded to assess the ability of these agents to prevent cardiovascular disease and cancer in a 2x2 randomized, double-blind, placebo-controlled factorial trial among 20,000 men and women, aged ≥60 and ≥65 years, respectively.

VITAL-DEP is an ancillary study of VITAL (IRB # 2009P001217); all participants will be members of the main VITAL protocol. The VITAL-DEP protocol is intimately linked to the VITAL protocol that already been IRB approved. We present here only activities that are part of the VITAL-DEP study. As with the parent proposal, we are asking for IRB review of our protocols in segments, and this application is for the FULL cohort portion of VITAL-DEP, which involves all 20,000 VITAL participants. For details please see RESEARCH DESIGN AND METHODS.

Specifically, we propose to evaluate the following aims:

PRIMARY AIMS

1. We will test whether vitamin D_3 (cholecalciferol: 2000 IU/d) or marine omega-3 (EPA: 500 mg/d + DHA: 500 mg/d) supplementation reduces risk of incident and recurrent clinical depressive syndrome compared to placebo among all 20,000 participants in the VITAL trial.

2. We will test whether vitamin D_3 (cholecalciferol: 2000 IU/d) or marine omega-3 (EPA: 500 mg/d + DHA: 500 mg/d) supplementation yields better continuous mood scores on repeated measures compared to placebo among all 20,000 VITAL trial participants over the 5-year study period.

SECONDARY AIMS

1. Response to D_3 among African-Americans in the VITAL cohort:

a. We will test whether African-American race modifies effects of vitamin D3 supplementation on late-life depression risk and on mood scores among all VITAL participants (African-Americans, who will be over-sampled and will represent 25% of the VITAL study population, are disproportionately affected by vitamin D insufficiency).

2. Response to D_3 and EPA+DHA among key clinical subgroups in the CTSC sub-cohort:
a. We will test whether individuals at high risk for depression (e.g., elevated anxiety, physical functional impairment, chronic medical illness, living without partner) will demonstrate lower 2-year risk of clinical depressive syndrome and depression scores over 2 years on active agent vs. placebo.
b. We will test whether individuals with subsyndromal depressive symptoms will demonstrate lower 2-year risk of major depressive disorder and depression scores over 2 years on active agent vs. placebo. **NOTE: A separate IRB application will be submitted for the CTSC sub-cohort portion.**

3. Response to D_3 and/or EPA+DHA by baseline plasma biomarker levels in a nested case-control sample:
a. We will test whether low baseline vitamin D and EPA+DHA levels will be associated with elevated risk of clinical depressive syndrome and worse depression scores over 5 years in the full VITAL cohort.
b. We will test whether effects of vitamin D_3, and of EPA+DHA, on risk of clinical depressive syndrome and on depression scores will be modified by baseline plasma levels of vitamin D, and of EPA+DHA, respectively.

EXPLORATORY AIMS – we will address whether:
a. Combined vitamin D_3 and EPA+DHA will exert synergistic or additive effects on risk of clinical depressive syndrome and on depression scores over time;
b. Effect of vitamin D_3 or EPA+DHA supplementation will vary by (1) age, (2) gender, (3) baseline intakes of vitamin D and omega-3, (4) baseline major medical comorbidities, (5) geographic region/latitude (for vitamin D_3), and (6) physical activity (for vitamin D_3).

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Despite much progress in the treatment of mood disorders, depression continues to be a leading cause of disease burden and disability for millions of older Americans. VITAL-DEP proposes to leverage the strengths of the VITAL (1 U01 CA138962; IRB # 2009P001217) 2x2 factorial cancer and heart disease prevention trial using vitamin D_3 and marine omega-3 fatty acid (ω-3) supplementation among 20,000 men and women aged ≥60 and ≥65 years, respectively, and to implement procedures to estimate the effects of these agents on mood and risk of late-life depression; VITAL also includes a sub-cohort of 1,000 participants recruited to a Clinical and Translational Science Center (CTSC). Biologic and observational data support potential mental health benefits of both vitamin D and omega-3 fatty acids. However, it remains unclear whether these supplements can prevent onset of late-life depression or significantly reduce late-life depressive symptoms.

VITAL-DEP will have adequate sample size and statistical power to address both primary (incidence) and secondary prevention (recurrence) of depression and to utilize all modalities of state-of-the-art prevention research: universal, selective and indicated. Findings from this proposed study will clarify whether these agents reduce risk of late-life depression and depressive symptoms, and will provide important data that will be applicable to public health and clinical guidelines for both primary and secondary prevention of depression.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

VITAL-DEP is an ancillary study of VITAL (IRB # 2009P001217). The VITAL-DEP protocol is intimately linked to the VITAL protocol that already been IRB approved. As with the parent proposal, we are asking for IRB review of our protocols in two segments. In the first stage of this application, we are seeking permission for the following activities that involve the **FULL cohort of VITAL**:

1. Receive updated data from the main VITAL parent trial regarding responses to the VITAL mood questionnaire items.
2. Conduct enhanced telephone follow-ups with and send letters to VITAL participants who meet an algorithmic threshold for clinically significant depressive symptoms on the VITAL mood questionnaire.
3. Receive updated data from the main VITAL parent trial (via CMS [Centers for Medicare and Medicaid Services] contractor) regarding evaluations, diagnoses and treatments related to mood disorders (including depression) and other Diagnostic and Statistical Manual-IV (DSM-IV) disorders.
4. Conduct biomarker analyses of baseline plasma vitamin D (25-hydroxy-vitamin D [25(OH)D]) and EPA and DHA acid levels among a subset (n=1,500) of the 20,000 VITAL participants, in a nested case-control design, using pre-randomization blood samples collected by the main VITAL study.

In parallel with the main VITAL study, in this application we are not applying for permission perform the CTSC component (which will have its own separate IRB application). In the separate CTSC IRB application we will seek permission for all CTSC protocol activities, with detailed descriptions of the protocols and human subject protection issues. This present summary will include brief descriptions of the portions of the protocol for which we will seek IRB approval in the later application.

Study Design:

We will conduct an ancillary study of depression within the VITAL trial (VITAL-DEP). VITAL-DEP will be a randomized, double-blind, placebo-controlled 2x2 factorial clinical trial among 20,000 men and women, respectively aged ≥60 and ≥65 years. All participants in VITAL-DEP will be participants in the main VITAL trial (IRB # 2009P001217) and will be followed up for 5 years. We will assess primary outcomes of the effects of the agents on prevention of incident and recurrent late-life depression as well as benefits of the agents on continuous mood scores. The depression endpoint ("depression") in VITAL-DEP will be defined as any clinically significant depressive syndrome. This combined depression endpoint will include the following DSM-IV and International Classification of Disease-9 (ICD-9) diagnoses: major depressive disorder (MDD), dysthymia, adjustment disorder including depressed mood, and depressive disorder not otherwise specified (NOS).

Anticipated enrollment:

Up to 20,000 men and women, respectively aged ≥60 and ≥65 years – the full complement of the VITAL cohort – may be enrolled. However, given expected current prevalence of depression in this population (which was informed by the available gender-, age- and ethnicity-specific evidence), we anticipate that 18,200 persons will meet the additional eligibility criteria for VITAL-DEP (see below).

Eligibility criteria:

Participants in VITAL-DEP will be enrolled from across the US by mailed questionnaires.

Participants in VITAL-DEP will meet the criteria for eligibility of the main VITAL trial: (1) men aged aged ≥60 years and women aged ≥65 years, (2) have at least a high school education (to complete mail-based questionnaires); (3) have no history of cancer (except non-melanoma skin cancer), MI, stroke, TIA, angina pectoris, CABG, or PCI; (4) have none of the following safety exclusions: history of kidney stones, renal failure or dialysis, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases, such as active chronic tuberculosis or Wegener's granulomatosis; (5) have no allergy to fish (for DHA+EPA); (6) have no other serious illness that would preclude participation; (7) are consuming no more than 800 IU of vitamin D from all supplemental sources combined (individual vitamin D supplements, calcium+vitamin D supplements, medications with vitamin D [e.g., Fosamax Plus D], and multivitamins), or if taking, willing to decrease or forego such use; (8) are consuming no more than 1200 mg/d of calcium (the RDA for individuals aged >50) from all supplemental sources combined, or if taking, willing to decrease or forego such use during the trial; (9) are not taking fish oil supplements, or if taking, willing to forego their use during the trial; and (10) are willing to participate, as evidenced by signing the informed consent form.

In addition to the above criteria, VITAL-DEP will have additional eligibility criteria. Additional exclusions for VITAL-DEP are: 1) current significant depressive symptoms; 2) self-reported history of dysthymia with active dysthymic symptoms in the past one year; 3) self-reported core major depressive disorder symptoms for a period of two or more weeks in the past two years; 4) any history of alcohol and/or substance abuse disorder active in the past 12 months, schizophrenia or other primary psychotic disorder, bipolar disorder, post-traumatic stress disorder or obsessive-compulsive disorder; 5) any psychiatric hospitalization in the past 2 years; 6) current psychotherapy or use of psychotropics (including non-prescription drugs or herbals for treatment of mood disorders), except for limited use of mild sedatives/hypnotics; 7) history of major neurologic disorder (e.g., Parkinson disease, Alzheimer disease or other dementia, brain tumor, seizure disorder) or delirium episode in the past 12 months.

Local site restrictions:
Participants in VITAL and VITAL-DEP will be enrolled from across the US by mailed questionnaires; thus there is no local site recruitment.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Study procedures:

1) Enrollment: The participants of VITAL will be enrolled by a screening questionnaire. Those who are screened receive another questionnaire that includes questions on nutrition and supplement use, health history, and willingness to participate in blood draws ("Would you be willing to provide a blood sample if we sent you a convenient collection kit containing everything you need?").

2) Run-in: Those who meet the basic VITAL eligibility criteria will then undergo a run-in period to identify the excellent compliers. In this period, all participants will be given placebo vitamin D and placebo fish oil and assessed on compliance and willingness to continue. In addition, all participants will be asked for blood samples and completion of questionnaires on diet and depression (as part of the main VITAL protocol).

Importantly, using the mood items on the run-in questionnaires, we will ascertain current and past history of depression symptoms, diagnoses and/or treatments. This information (supplemented by information from CMS) will be used to determine eligibility for VITAL-DEP.
To perform follow-ups for VITAL participants scoring above established cutoffs for the PHQ-8, we will adhere to a hierarchical approach to follow-up contacts, optimizing feasibility, timeliness and contact coverage of our participants. First, we will be sending letters to all VITAL participants who score above the PHQ-8 ≥10 algorithmic cutoff, where there is no self-report by the participant of both recent diagnosis and treatment of depression on the questionnaire or an indication of such from the CMS data. These letters serve to educate participants about the presence of mood problems that could include depression and to encourage them to discuss their mood with their health provider; the letters also provide contact information should the participants wish to speak with study investigators about the letter. Data computer programmers will be able to determine such status as soon as returned questionnaires are processed into the system, triggering generation of the follow-up letters. We have composed three letters to cover all participants in the VITAL study who return responses to the PHQ-8: 1) those who are subsequently randomized to active study pills, 2) those who are later determined to be ineligible for VITAL, and 3) those who indicate unwillingness to continue future involvement in the study. A key goal is to ensure that participants are educated about the need to discuss their mood with their local providers and, thus, initiate a path for ongoing evaluation and/or treatment as necessary; thus, among participants who are randomized and continue in the study, we will only conducts these contacts when participants first report above-threshold scores. These letters will also be sent to any participant who scores above the threshold for clinically significant depressive symptoms on the PHQ-8 (≥15) (N.B.: work by the developers of the PHQ-8 indicates likely depression of moderate-to-severe degree at this score), regardless of whether they report recent depression diagnosis or treatment, or whether they have any core features (depressed mood or anhedonia) in the PHQ algorithm. We feel that this step is important: although some individuals with PHQ-8 scores ≥15 may not meet DSM-IV criteria for major depression, persons with such symptoms may be at increased risk of poor outcomes if their symptoms go unrecognized and/or untreated and/or under-treated.

3) Randomization: Those who demonstrate good compliance and a willingness to continue with the 2x2 factorial trial will be randomized by VITAL.

4) Follow-up data collection:
A. Self-reported symptoms (PHQ-8) as well as diagnoses and treatment(s) will be ascertained from responses on the VITAL baseline (year 0) and follow-up questionnaires (years 1, 3 and 5).

B. On an annual basis, CMS data diagnoses and treatments related to depression and/or other mental disorders will be ascertained with the assistance of VITAL's CMS contractor ResDAC (www.resdac.unm.edu/Index.asp).

C. The combination of the above follow-up data (self-reports on the VITAL questionnaires and CMS data) will be used to ascertain the depression endpoint.

5) Biochemical analyses of baseline vitamin D and omega-3 fatty acids will be conducted on blood samples collected as part of the main VITAL protocol. Participants will comprise a nested case-control study and will be selected from among VITAL participants with baseline, pre-randomization blood samples (as part of the main VITAL protocol). Blood levels of 25(OH)D and marine omega-3 fatty acids (DHA+EPA) will be assayed on 500 cases of depression and 1,000 controls matched on 5-year age group, gender, follow-up time and season of blood draw. Circulating 25(OH)D will be determined by radioimmunoassay, and DHA and EPA will be quantified using a high-throughput method that employs fast gas chromatography and robotic transesterification to achieve high fatty acid methyl ester (FAME) resolution. VITAL-DEP will only use the existing blood samples collected by VITAL, and will not solicit or collect any additional blood samples from participants.

6) Statistical analysis to evaluate the specific aims. The primary study endpoints are: 1) relative risks of incident and recurrent depression and 2) trajectory of mood scores over time. Secondarily, we will

assess: 1) impact of vitamin D_3 supplementation on depression risk among African-Americans (who are at increased risk of vitamin D insufficiency), 2) impact of both agents among clinical sub-groups at high risk for depression (CTSC sub-cohort; separate IRB application), and 3) impact of baseline plasma vitamin D and marine omega-3 levels on depression risk in a nested case-control sample of 1,500 participants. Finally, we explore potential interactions of the agents with key modifiers.

7) Manuscript preparation, submission and publication.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

This study does not involve treatment or diagnosis of participants. We will not be performing clinical assessments of mood and/or other disorders, but rather will be obtaining self-reports of depressive symptoms and diagnoses from participants, as well as CMS data on diagnoses and treatments already performed by their health providers.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

There is the possibility of social/psychological risk that could result from inadvertent disclosure of confidential information. However, we have many safeguards in place to avoid this possibility, and we have never had an inadvertent breach of confidentiality in any of the previous trials in the BWH Division of Preventive Medicine (the "Division") that is running the VITAL trial.

The potential risk of disclosure of confidential information is guarded against by maintaining data, questionnaires and forms in locked files accessible by authorized personnel only. In these files, participants are identified only by study ID. Subject identifiers are stored in separate computer files with password protection, and results will be presented only in the aggregate. In addition, employees involved with the proposed study will be asked to sign a form agreeing not to disclose any information to which they might have access, regardless of their personal perception about its confidentiality. Each employee of the study with human subject contact participates in an institutional (Brigham and Women's Hospital) human subjects educational program, which consists of reviewing regulatory and informational documents pertaining to human subjects research; passing a test on ethical principles and regulations governing human subjects research; and signing a statement of commitment to the protection of human subjects. Finally, all such employees are required to participate in HIPAA training.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

To further enhance the safety of our participants, we will be sending letters, as detailed above, to those who score above the PHQ-8 ≥10 algorithmic cutoff, where there is no self-report by the participant of both recent diagnosis and treatment of depression or an indication of such from the CMS data; further, we will be sending the letters to any participant who scores at or above PHQ-8 of 15, regardless of recent diagnosis and/or treatment for depression by self-report. We feel that this

step is important: although some individuals with PHQ-8 scores ≥15 may not meet DSM-IV criteria for major depression, persons with such symptoms may be at increased risk of poor outcomes (including self-harm) if depression goes unrecognized and/or untreated and/or under-treated. As noted above, the letters also provide contact information should the participants wish to speak with study investigators about the letter. Thus, the VITAL-DEP RA, working under the direction of the PI, will work with data programmers to coordinate the send-out of the letters and to track the letters and any participant responses, comments or questions pertaining to the letters.

Other methods for insuring subjects' safety, removing subjects from the study and the DSMB review of adverse events (including mental health-related events, such as suicidal behavior) are all part of the main VITAL trial. The only additional risk in participating in VITAL-DEP is risk to subjects' privacy (please see above section on minimizing risks).

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

There is the possibility of social/psychological risk that could result from inadvertent disclosure of confidential information. However, we have many safeguards in place to avoid this possibility, and we have never had an inadvertent breach of confidentiality in any of the previous trials in the Division, which is overseeing VITAL.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

For the majority of participants, there will be few direct benefits from participating in this primary prevention study other than the awareness of being involved in a large endeavor to answer relevant and timely questions regarding the possible benefit of vitamin D and fish oil.

During the trial itself, we will receive inquiries from the participants regarding both specific and general health concerns. We will respond to each of those questions, primarily directing participants to published sources or recommending that they see their local health provider who is familiar with their medical history. In addition, participants may benefit from the enhanced follow-up of those reporting high levels of depressive symptoms. Many such persons might not otherwise be referred to their local providers for further evaluation and management of depression.

The purported health benefits of vitamin D and marine omega-3 fatty acids are receiving increasing attention in the medical literature and the popular press. Sales of vitamin D supplements and omega-3 fatty acid supplements at U.S. stores have increased substantially in recent years. However, definitive data on health benefits and risks of these agents are lacking. Findings from this large clinical trial will clarify the role of vitamin D and marine omega-3 fatty acid supplements in the prevention of depression will help guide individual decisions, clinical recommendations, and public health guidelines.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The gender distribution of the 20,000 participants in VITAL will be 50% male and 50% female—specifically, 10,000 men aged ≥60 and 10,000 women aged ≥65.

Based on the VITAL pilot results, we expect the following ethnic distribution: 1,400 (7%) Hispanic and 18,600 (93%) non-Hispanic; with regard to race, we anticipate 5,000 (25%) African-American, 500 (2.5%) Asian, 400 (2%) American Indian (Native American), 80 (0.4%) Pacific Islander, and 14,020 (70.1%) white individuals. Note that ethnic and racial categories can overlap—e.g., participants can be Hispanic-white or Hispanic-black.

The outcomes to be studied, incident and recurrent late-life depression, were selected for this prevention trial because they represent major causes of disease burden and disability in older men and women. Furthermore, as the funded parent VITAL study, with which the proposed VITAL-DEP ancillary is associated, does not include participants under the age of 60 years, children and adolescents were not included in the VITAL-DEP proposal. Finally, there are limited data available regarding the efficacy and safety of vitamin D and omega-3 fatty acids as depression prevention agents in adults; it would therefore be preferable to obtain more adult data prior to testing these agents in younger children. As there are other treatments (i.e., non-medication treatments, or psychotherapies) available for children and adolescents at risk for depression, exclusion of children from this study should not prevent them from obtaining appropriate care.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

The participants in VITAL will be English speaking/ English proficient. It is not our intention to exclude non-English speaking participants. Indeed, the mood items we are utilizing (e.g., the PHQ) and will be on the VITAL questionnaires have been translated into several languages or are readily translatable. However, because our VITAL-DEP participants will all be part of the VITAL trial, we expect that they will all be English speaking/proficient.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

20,000 men and women, respectively aged ≥60 and ≥65 years will be recruited into VITAL. All of our participants will come from the VITAL cohort. However, given expected current prevalence of depression in this population (which was informed by the available gender-, age- and ethnicity-specific evidence), we anticipate that 18,200 persons will meet the additional eligibility criteria for VITAL-DEP and will be eligible for our analyses of depression prevention.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

There is no compensation for participating in VITAL-DEP.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

VITAL-DEP participants will have provided informed consent for participation in VITAL using the approved procedure ((IRB # 2009P001217). As part of the VITAL informed consent procedure, participants will already be notified that study investigators may need to contact them directly with regard to development of endpoints and also to obtain releases to contact their local health providers. No additional informed consent procedures are planned for VITAL-DEP participants beyond those of VITAL. Standard releases of medical information will be required to be signed by participants in order to communicate with their local health providers, except in the case of an emergency (such as suicidal ideation with imminent threat of self-harm). VITAL participants may decline their participation in VITAL at any time and can refuse at any time to answer (leave blank) items on mood or depression on the questionnaires.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

An independent Data and Safety Monitoring Board (DSMB) will be assembled, consisting of experts in clinical trials, epidemiology, biostatistics, relevant clinical areas of cancer and CVD, cognitive function and NIH representatives. The Physicians' Health Study, the Women's Health Study, and the Women's Antioxidant and Folic Acid Cardiovascular Study (the main trials as well as ancillary outcome studies) have been monitored by the same DSMB since their inception. As two of these trials have ended and the third is in its last years, we will ask our DSMB members if they would be willing to also monitor VITAL. If they are not able to do so, we will consult with them in assembling a new DSMB. Current VITAL DSMB members are Drs. Lawrence S. Cohen, Theodore Colton, Mark A. Espeland, I. Craig Henderson, Alice H. Lichtenstein, Rebecca A. Silliman, and Nanette Wenger (chair). Ex officio members are Drs. Josephine Boyington (NHLBI), Rebecca B. Costello (ODS), Cindy D. Davis (NCI), Peter Greenwald (NCI), and Lawrence Fine (NHLBI). In addition, we will nominate experts in depression clinical trials and psychiatric outcome measurement to the VITAL DSMB. The DSMB Chair has strongly endorsed the importance of such experts on the DSMB, and their presence will ensure a high level of acumen for monitoring differences in depression by treatment arm.

The VITAL Data and Safety Monitoring Board (DSMB) will be charged with ensuring that the safety of participants is protected and that the scientific goals of the study are being met. The VITAL DSMB will include psychiatric expertise and will monitor differences by treatment arm of ancillary study outcomes, including depression, and will be empowered to terminate the trial based on evidence of substantial harm or benefit. To support those purposes, the DSMB will review any proposed amendments to the study protocol, examine the progress of the trial and the unblinded data on study endpoints, perform expedited review of all serious adverse events (i.e., events meeting the FDA definition of Serious Adverse Events, such as any fatal event including suicide, immediately life-threatening event, or permanently or substantially disabling event), perform ongoing

monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of participants, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure participant privacy and research data confidentiality.

The DSMB will annually examine the progress of the trial and the unblinded data on study endpoints and possible adverse effects to recommend continuation, alteration of study design, or early termination, as appropriate. Interim trial results will be assessed with the Haybittle-Peto rule, adjusting for multiple looks. In this method, interim results are compared to a z-score of 3 standard deviations (p=0.0027) throughout the trial. The final results may then be interpreted as having close to nominal significance levels. This rule appropriately requires very strong evidence for early stopping, is more conservative than the Pocock and O'Brien-Fleming rules and the alpha-spending function, and can be conducted at convenient times without inducing statistical complexity. The monitoring rules will serve solely as guidelines in decisions regarding continuation or stopping of treatment arms. All decisions will be made after examining the totality of evidence, including other trial data, on these agents.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The DSMB will annually examine the progress of the trial and the unblinded data on study endpoints and possible adverse effects to recommend continuation, alteration of study design, or early termination, as appropriate.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

All research forms (e.g., VITAL questionnaires) will be scanned in and the data read by a character recognition software program (Teleform). Out-of-range, internally inconsistent, and unclear data will be reviewed by a verifier who will edit misread variables. Forms that cannot be scanned will be entered using traditional double-entry procedures. All data will undergo additional within form and across-time checks to verify accuracy. Following data entry, all questionnaire responses that require

additional follow-up for missing data, participant comments on the form or for endpoint validation will be manually reviewed to insure correct processing and accurate follow-up.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

The potential risk of disclosure of confidential information is guarded against by maintaining completed questionnaires and blood test results in locked files accessible by authorized personnel only. Depression endpoint and mental health-related questionnaire data will be stored in separate files from the processing data and will be accessible only to approved investigators and programmers. In these files, participants are identified only by study ID. Subject identifiers are stored in separate computer files with password protection, and results will be presented only in the aggregate. Subject identifiers will retrieved only by approved and trained personnel for the purposes of making enhanced safety telephone follow-ups. Each dataset will require documentation with information about the methodology and procedures used to collect the data, details about codes, definitions of variables, variable field locations, frequencies, etc. The precise content of documentation will vary by scientific area and characteristics of the dataset. Participants' names and contact information will be accessible only to staff members who need the information for their jobs. In addition, employees involved with the proposed study will be asked to sign a form agreeing not to disclose any information to which they might have access. Each employee of the study with human subject contact participates in an institutional (Brigham and Women's Hospital) human subjects educational program, which consists of reviewing regulatory documents; passing a test on ethical principles and regulations governing human subjects research; and signing a statement of commitment to the protection of human subjects. Finally, employees are required to obtain HIPAA training. Thus, our existing computer and security systems balance considerations of careful follow-up and high levels of data security and privacy protection.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent,

and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Blood samples will be sent to the laboratory of Dr. Bruce at the Medical University of South Carolina in Charleston (a Consultant on the VITAL parent grant) for measurement of circulating 25(OH)D. Blood samples will be sent to the laboratory of Cdr. Dr. Joseph Hibbeln at the Laboratory of Membrane Biophysics and Biochemistry (LMBB), NIAAA, NIH for measurement of plasma fatty acids. Per standard practice, hospital-approved Material Transfer Agreements (MTAs) will be required of these Collaborators before specimens can be transferred. All the blood samples will be provided in non-identifiable form such that links to identifiable humans do not exist.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Specimens/data will not be stored at outside collaborating sites.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

We will not receive specimens/data from outside collaborators.

I. BACKGROUND AND SIGNIFICANCE

Depression is among the most disabling of all health conditions. By 2020, depression will nearly top the list of global causes of disability – second only to heart disease[1-3]. Depression in late-life, in particular, is strongly associated with increased morbidity, health care utilization, and costs[4]. Thus, prevention of late-life depression is a public health priority. The VITAL (*VIT*amin D and Omeg*A*-3 Tria*L,* 1 R01 CA 138962) study, which will investigate effects of vitamin D and marine omega-3 polyunsaturated fatty acid (ω-3 PUFA) supplements on heart disease and cancer prevention among 20,000 men and women (aged ≥60 and ≥65 years, respectively) presents a novel opportunity to conduct the first large-scale randomized controlled trial of primary and secondary prevention of late-life depression. The proposed study will test whether long-term use of vitamin D and/or marine ω-3 PUFAs can reduce the risk of depression, as well as levels of depressive symptoms, among older adults. VITAL-DEP also provides an opportunity to conduct a study with sufficient sample size and statistical power[5] to test simultaneously agents for universal, selective and indicated prevention of depression[6].

Recent observational data support an association between low vitamin D levels and depressed mood among older people. In one large study[7], serum 25(OH)D levels were significantly lower in depressed vs. non-depressed elders, and depression scores were significantly inversely associated with vitamin D levels. Trial data on vitamin D supplementation and depressive symptoms have produced mixed results[8, 9], and have featured important limitations[10], including small sample size and likely insufficient treatment dose/duration. Overall, there are growing suggestions that a large-scale depression prevention trial of vitamin D – especially among older people, who are at high risk for vitamin D deficiency – is an idea whose time has come.[10, 11] In addition, African-Americans are a particularly important group among whom to investigate this question, as they tend to have lower vitamin D levels than Caucasian-Americans.[12, 13] African-Americans are also overrepresented among those with severe and disabling depression[14] – yet simultaneously face significant barriers to evaluation and treatment of depression, particularly at late-life.[15, 16] Thus, any late-life depression trial of vitamin D_3 would need to consider potential impact for African-Americans.

Depression has been inversely related to marine ω-3 PUFA and fish intake in many[17-22] but not all[23-26] larger-scale observational studies with cross-sectional design. However, there are no prospective data yet from large-scale observational studies regarding marine ω-3 PUFAs and depression. There have been several randomized single- or double-blind clinical trials investigating marine ω-3 PUFAs and non-bipolar depression in adults[27-35]. These trials have suggested likely antidepressant effects of marine ω-3 PUFAs, especially as adjunctive therapy. However, limitations[36, 37] of prior RCTs include: 1) relatively small sample size (n<100), 2) short-term follow-up (≤6 months), 3) insufficient power to address racial/ethnic differences, or 4) having few older participants. Furthermore, participants in all but two[31, 35] trials were from clinical populations, with existing depressive disorders; most studies involved augmenting existing antidepressant therapy with marine ω-3 PUFAs. There are no data from large-scale randomized controlled trials regarding the use of marine ω-3 PUFA supplementation for prevention of clinical depression in generally healthy adults.

We propose an ancillary study to evaluate the critical health endpoint of depression within VITAL: VITAL-*DEP* (depression endpoint prevention). VITAL-*DEP* will utilize both categorical and continuous outcome measurements[15, 38] – taking maximal advantage of the larger VITAL study design. Incidence and recurrence rates of late-life clinical depressive syndromes and levels of depression symptom scores[39] will be the primary outcomes. In addition, VITAL-*DEP* will conduct an RCT of these trial agents among a random subset of 1,000 men and women – aged ≥60 and ≥65 years, respectively – who will be evaluated in-person at the four VITAL-affiliated Clinical and Translational Science Centers (CTSCs), using standard psychiatric interviews[40]. The CTSC sub-cohort participants will be administered psychiatric interviews at baseline, and again at two-year follow-up, facilitating our examination of treatment effects in well-characterized, key clinical subgroups.

II. SPECIFIC AIMS

PRIMARY AIMS

1. We will test whether vitamin D_3 (cholecalciferol: 2000 IU/d) or marine omega-3 (EPA: 500 mg/d + DHA: 500 mg/d) supplementation reduces risk of incident and recurrent clinical depressive syndrome compared to placebo among all participants in the VITAL trial.

2. We will test whether vitamin D_3 (cholecalciferol: 2000 IU/d) or marine omega-3 (EPA: 500 mg/d + DHA: 500 mg/d) supplementation yields better continuous mood scores on repeated measures compared to placebo among all VITAL trial participants over the 5-year study period.

SECONDARY AIMS

1. Response to D_3 among African-Americans in the VITAL cohort:
a. We will test whether African-American race modifies effects of vitamin D_3 supplementation on late-life depression risk and on mood scores among all VITAL participants (African-Americans, who will represent 25% of the VITAL study population, are disproportionately affected by vitamin D insufficiency).

2. Response to D_3 and EPA+DHA among key clinical subgroups in the CTSC sub-cohort:
a. We will test whether individuals at high risk for depression (e.g., elevated anxiety, physical functional impairment, chronic medical illness, living without partner) will demonstrate lower 2-year risk of clinical depressive syndrome and depression scores over 2 years on active agent vs. placebo.
b. We will test whether individuals with subsyndromal depressive symptoms will demonstrate lower 2-year risk of major depressive disorder and depression scores over 2 years on active agent vs. placebo.

3. Response to D_3 and/or EPA+DHA by baseline plasma biomarker levels in a nested case-control sample:
a. We will test whether low baseline vitamin D and EPA+DHA levels will be associated with elevated risk of clinical depressive syndrome and worse depression scores over 5 years in the full VITAL cohort.
b. We will test whether effects of vitamin D_3, and of EPA+DHA, on risk of clinical depressive syndrome and on depression scores will be modified by baseline plasma levels of vitamin D, and of EPA+DHA, respectively.

EXPLORATORY AIMS – we will address whether:
a. Combined vitamin D_3 and EPA+DHA will exert synergistic or additive effects on risk of clinical depressive syndrome and on depression scores over time;
b. Effect of vitamin D_3 or EPA+DHA supplementation will vary by (1) age, (2) gender, (3) baseline intakes of vitamin D and omega-3, (4) baseline major medical comorbidities, (5) geographic region/latitude (for vitamin D_3), and (6) physical activity (for vitamin D_3).

III. SUBJECT SELECTION

VITAL-DEP participants will be members of the full cohort (n=20,000) of VITAL (IRB # 2009P001217) who meet all inclusion and exclusion criteria for VITAL and also satisfy additional exclusion criteria for the depression prevention study. In general, participants with a history of psychiatric disorders apart from depressive disorders will be excluded. Detailed exclusions are: 1) current significant depressive symptoms; 2) self-reported history of dysthymia with active dysthymic symptoms in the past one year; 3) self-reported core major depressive disorder symptoms for a period of two or more weeks in the past two years; 4) any history of alcohol and/or substance abuse disorder active in the past 12 months, schizophrenia or other primary psychotic disorder, bipolar disorder, post-traumatic stress disorder or obsessive-compulsive disorder; 5) any psychiatric hospitalization in the past 2 years; 6) current psychotherapy or use of psychotropics (including non-prescription drugs or herbals for treatment of mood disorders), except for limited use of mild sedatives/hypnotics; 7) history of major neurologic disorder (e.g., Parkinson disease, Alzheimer disease or other dementia, brain tumor, seizure disorder) or delirium episode in the past 12 months.

Details on ascertainment of these exclusion variables for the full VITAL cohort are provided below. The procedures for the entire full cohort VITAL study have been IRB-approved (IRB # 2009P001217).

For the CTSC sub-cohort (n=1,000) described in Secondary Aim 2, a separate IRB application will be submitted. As there a numerous planned ancillary studies to VITAL (including the current VITAL-DEP application), a single IRB for the entire CTSC protocol – including all detailed assessment and safety procedures for VITAL-DEP – has been separately prepared for submission by VITAL.

IV. SUBJECT ENROLLMENT

VITAL-DEP participants will consist only of those participants who have already been enrolled in VITAL (IRB # 2009P001217). Thus, VITAL-DEP will have the identical enrollment procedure. The IRB-approved enrollment procedure for VITAL is as follows:

1) Enrollment: Participants in VITAL will be enrolled from across the US by mailed screening questionnaires.

2) Run-in: Those who meet the basic eligibility criteria will then undergo a run-in period to identify the excellent compliers. In this period, all participants will be given placebo vitamin D and placebo fish oil and assessed on compliance and willingness to continue. In addition, all participants will be asked for blood samples (as part of the main VITAL protocol). Importantly, the VITAL run-in questionnaires will include questions on history of current and past depression symptoms, diagnosis and treatment.

3) Randomization: Those who demonstrate good compliance, a willingness to continue with the 2x2 factorial trial will be randomized.

V. STUDY PROCEDURES

1) Overview.
The depression endpoint ("depression") in VITAL-DEP will be defined as any clinically significant depressive syndrome[41]. This combined depression endpoint will include the following Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[42] and International Classification of Disease-9 (ICD-9) diagnoses: major depressive disorder (MDD), dysthymia, adjustment disorder including depressed mood, and depressive disorder not otherwise specified (NOS). As depressive syndromes – even those that do not meet criteria for MDD – can have significant impact on morbidity[43, 44], we chose not to restrict our endpoint to DSM-IV-defined MDD. Use of such composite endpoints of highly-related outcomes is common in large prevention trials[45-48], and has also been utilized in studies of incident late-life depression[49].

2) Measures and sources of information for depression status determination in the full VITAL cohort.
All VITAL participants will receive questionnaires at baseline, and at follow-up years 1, 3 and 5, that include the Patient Health Questionnaire-8 (PHQ-8)[39]. See mood questions in Appendix (VITAL 3).

Patient Health Questionnaire-8. The PHQ-8 was developed for detection of depression in primary care and community-based settings. It is identical to the PHQ-9[50] with the exception of the item on suicidal ideation and behaviors[39, 51]. Prior validation work in >6,000 participants established that elimination of this item has no impact on the ability of the PHQ-8 to classify depression and that identical scoring thresholds for depression can be used[52]. We chose to delete this item after careful consideration of potential consequences. VITAL will mail questionnaires to thousands of participants around the country, and the time lag between questionnaire

send-date and post-receipt data processing is usually several weeks to months. Thus, we would not be able to identify a positive response to suicide inquiry in a reasonable period of time. We believe that adding this item could create a false expectation of a rapid response, as many participants might reasonably expect that investigators would not make such an inquiry unless they intended to respond immediately. Consequently, safety could actually be compromised, as participants could be induced to wait months for an investigator response, rather than contacting health providers or supportive persons promptly with such symptoms. To best protect participant safety, we worked with the VITAL parent trial investigators to modify the VITAL questionnaire to include language informing all participants that if any of the questions raise their level of awareness or concern about depression or mood, then they should promptly contact their health providers. Also see "Enhanced follow-up procedures."

After careful review of other available self-report instruments (e.g., CES-D[53], Geriatric Depression Scale[54], BDI[55]), the PHQ-8 was selected for VITAL-DEP for the following reasons: 1) it has validity for identifying depression in the context of medical comorbidity, including heart disease – thus, earning the joint endorsement of the American Heart Association and American Psychiatric Association for depression screening in this context[56]; 2) it has been validated against "gold-standard" interviews, such as the Composite International Diagnostic Interview (CIDI)[57] and Structured Clinical Interview for DSM-III-R (SCID)[58]; 3) a validated algorithm can be used to determine whether a respondent meets criteria for MDD or other depressive disorder[39]; 4) continuous PHQ scores (range=0-24) provide a severity measure (with scores ≥15 and ≥20 signaling moderate-high and high severity, respectively)[59] and are sensitive to change[60]; 5) it has been validated in cross-cultural settings and among community-dwelling elderly from diverse populations similar to that of VITAL[61-63], and shows no evidence of differential item functioning (also called item bias) among African-Americans and other minorities[64, 65] – which has been detected with other instruments[66-68]; 6) it is very brief and minimizes participant burden, and given the need to address multiple health, disease, demographic, and lifestyle characteristics in all VITAL participants – while minimizing total VITAL questionnaire length (it is only 2 double-sided pages) – the high information yield-to-space use ratio of the PHQ-8 is a key strength.

Diagnostic Interview Schedule (DIS)[69]. Two items from the DIS will be included; these have been selected for use in other ancillary studies of large-scale RCTs, such as the WHI[70], to detect symptoms of MDD and dysthymia. These questions will allow us to establish whether individuals with a history of depression have had clinical depression in the past 2 years – to better ensure inactive depression status and to identify persons who have had symptoms consistent with dysthymia at any point in their lives, including currently. See VITAL 3.

Global questions. We will ask participants two global questions on prior clinical diagnosis and medication and/or counseling treatment of depression. These items are adapted from questionnaires that have been utilized for over 20 years in the Nurses' Health Study (NHS) cohort involving >100,000 participants to demonstrate strong relations of depression to numerous health outcomes[71, 72]. See VITAL 3.

3) Additional information from the Centers for Medicare and Medicaid Services (CMS).
A critical advantage of VITAL that will be leveraged in the proposed VITAL-DEP study is linkage to the CMS inpatient and outpatient databases. We will annually obtain Medicare data with free assistance by ResDAC (www.resdac.unm.edu/Index.asp), a CMS contractor. We will carefully adhere to the data use agreement that delineates confidentiality requirements of the Privacy Act (HIPAA) and data release policies and procedures. The VITAL data coordinating center will: ensure data integrity and confidentiality, secure access to the CMS data storage cabinets, and utilize a password-protected logon policy.

The following CMS data files will be utilized: 1) Medicare Provider Analysis and Review (MedPAR) Inpatient and Skilled Nursing Facility File: contains inpatient records summarizing all services rendered from admission through discharge, and includes diagnoses and procedure codes, DRG, dates of service, hospital /SNF provider and beneficiary demographics; 2) Outpatient Standard Analytical File (SAF): contains final action

claims data from hospital outpatient departments, rural clinics, outpatient rehabilitation facilities, community mental health centers and other ambulatory centers, and includes diagnosis and procedures codes, dates of service, outpatient provider numbers, and beneficiary demographics; 3) Part D Drug Event File: contains prescription data that enable CMS to administer the Part D benefit, and when a beneficiary fills a prescription under Medicare Part D, a prescription drug plan sponsor must submit a summary record to CMS. Additional CMS data on diagnoses, procedures, and service dates will be available on both Home Health and Carrier (e.g., non-institutional providers, including physicians, physician assistants, clinical social workers) SAFs.

ICD-9 codes will be used to identify depression (Table 3), medical comorbidities and exclusionary conditions: bipolar or psychotic disorders; alcohol or drug abuse/dependence (last 12 months); cognitive/behavioral disorders of childhood onset; unspecified or transient disorders, such as delirium[73] (last 12 months, as delirium can persist in 1/3 of elders after 6 months[74]); and any dementing disorder[73]. A complete list of codes that will be used is provided in Appendix C. A recent validation study[75] found "substantial agreement" (κ=0.67) between ICD-9-CM codes and medical records for depression diagnoses: sensitivity=56.6 and specificity=99.4; positive predictive value=92.8 and negative predictive value=94.4. Thus, as modest sensitivity of administrative data is the primary concern, self-reports will further enhance depression detection.

Table 1. ICD-9 Codes Identifying Relevant Depressive Disorders

Psychiatric disorders	**ICD-9**
Depressive disorders	296.2, 296.20-296.26, 296.3, 296.30-296.36, 300.4, 309.0-309.1, 309.28, 311
Major depressive disorder	296.2, 296.20-296.26, 296.3, 296.30-296.36
Dysthymia	300.4
Depressive disorder not otherwise specified	311
Adjustment disorder (including depressed mood)	309.0-309.1, 309.28

In addition to ICD-9 codes, the CMS data include Current Procedural Terminology (CPT)[76] codes. We will query the CMS database for the new appearance of relevant CPT codes for mental health evaluations and/or treatments. The range of common CPT codes for depressive disorders is: 90801-90829, 90846-90862, 90870, 90882, 90887, 96101, 99051, 99060, 99201-99255, 99304-99318. Thus, we will be able to utilize CMS data linkage to obtain all of the following: 1) appearance of an ICD-9 code for a depressive disorder; 2) psychiatric hospitalization and the associated ICD-9 code[77]; 3) outpatient mental health visits, for which ICD-9 diagnosis and CPT service codes will be available; 4) prescription of antidepressants and/or other psychotropics and fill dates. These codes can also be used to determine date of onset of depressive disorders (i.e., date of service).

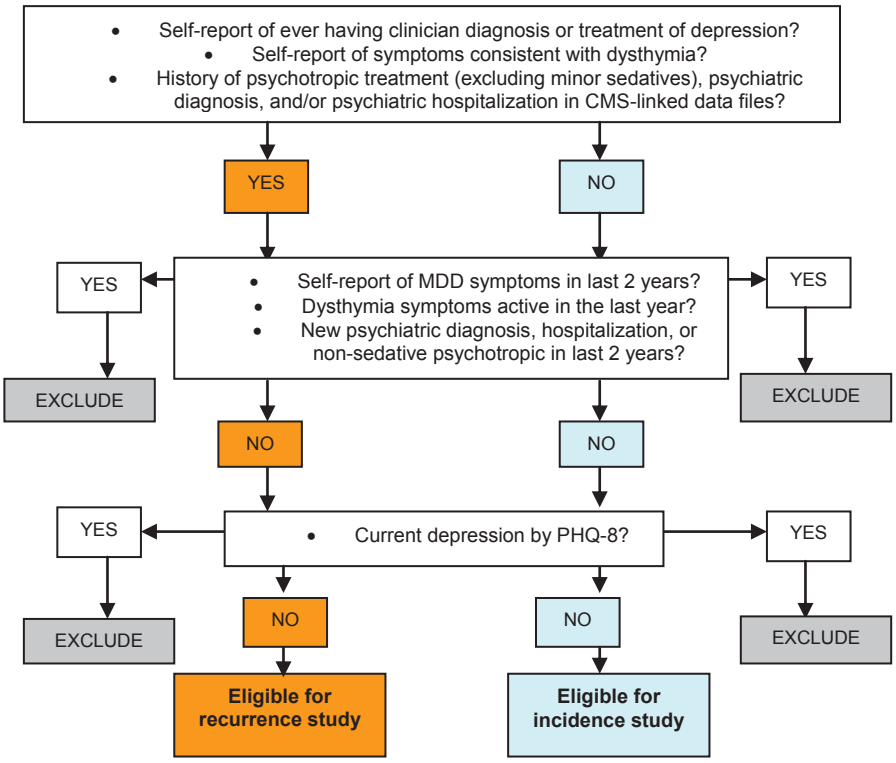
4) Rationale for eligibility scheme (see Figure below).
The PHQ-8 will be used to assess depressive symptoms experienced over the past two weeks. Thus, even among persons without a past history of depression diagnosis or treatment, it will be possible to exclude from the study of incidence rates those whose current symptoms meet the threshold for a depressive disorder. The combination of the PHQ-8, DIS items, global questions, and CMS data will enable us to determine which persons have had a past history of depression and, thus, may be eligible for study of recurrence rates.

5) Procedure for identifying incident depression.
We will utilize a strategy that: 1) employs existing methods for case-finding that have been successfully used in high-quality studies[41, 78, 79] involving large samples of community-dwelling elders and 2) enhances these methods with the rich CMS data at our disposal. On the baseline questionnaire supported by the parent VITAL trial, participants will complete the PHQ-8, as well as the DIS and global items. To supplement these self-reports, VITAL-DEP proposes to fund CMS data queries for ICD-9 and CPT visit codes consistent with the diagnosis of and/or treatment for a depressive disorder. A participant will be considered an incident case when any of the following occurs: 1) PHQ-8 symptoms of MDD or other depressive disorder by algorithm, 2) self-report of clinician diagnosis of depression, 3) self-report of DIS MDD symptoms, 4) self-report of DIS dysthymic

symptoms, 5) presence of ICD-9 code for depression during an inpatient or outpatient encounter, with or without a related mental health CPT code, 6) registration of prescription antidepressants. For any occurrence of the above, date of onset will be assigned as follows: 1) questionnaire received date for self-reports, 2) CMS visit date for clinician diagnostic codes, 3) dispense date of first antidepressant medication[41]. The earliest date will be used to define onset[41]. Of note, we chose to use the PHQ-8 algorithm, rather than the ≥10 point cutoff, as the algorithm can capture both MDD and other depressive disorders, which is consistent with our composite depression endpoint[39].

We will utilize a hierarchical approach[41] for determining depression status and onset when 2 or more sources of information indicate depression. Where available, the most specific method (e.g., ICD-9 code associated with a mental health CPT code) will be preferred for determining case status. The onset of depression will be that date which is linked to the preferred diagnosis method. When all methods are consistent with clinical depression, the earliest date will be used to define onset[41]. A Depression Endpoint Committee, consisting of Drs. Okereke, Chang, Reynolds and Mischoulon, and in consultation with Dr. Beekman, will arrive at consensus for all cases with conflicting reports from 2 or more sources.

Figure 1. Pathway for Determining Eligibility for Depression Incidence or Recurrence



<u>6) Procedure for identifying recurrent depression</u>.
A person will be counted as a recurrent case when any of the following occurs: 1) PHQ-8 symptoms consistent with MDD, 2) self-report of DIS MDD symptoms, 3) two consecutive-year self-reports of active dysthymia symptoms, 4) presence of a <u>new</u> mental health (CPT-coded) visit with linked ICD-9 code for depressive disorder during a clinical encounter, 5) hospitalization for depressive disorder, 6) <u>new</u> registration of prescription antidepressants. The hierarchal approach[41] to duplicate reports will be used. Notably, it is possible that incident cases of depression occurring early in follow-up can remit during the subsequent follow-up period. Technically, such persons – if remission is maintained for at least two years – could later become recurrent cases. However, we will not be "double-counting" of cases, as we wish to preserve original status from the time of the randomization. Thus, in analyses person-time will be counted from randomization until event or censoring; we will stop counting person-time after incident depression.

<u>7) Biochemical assays for VITAL-DEP</u>.
<u>Biochemical assays.</u> VITAL will conduct the pre-randomization blood collection from VITAL participants. VITAL-DEP proposes to fund all expenses related to assays of baseline 25(OH)D, EPA and DHA in 1,500 persons for a 1:2-matched nested case-control study of depression.

<u>Blood levels of 25(OH)D</u> will be assayed in the laboratory of Dr. Bruce Hollis at the Medical University of South Carolina in Charleston (a Consultant on the VITAL parent grant). Circulating 25(OH)D will be determined by

radioimmunoassay, as described elsewhere[80, 81]. The intra- and inter-assay coefficients of variation (CVs) are <10%. We will utilize NIST Standard Reference Material (SRM) for 25(OH)D_2 and 25(OH)D_3 measurements (SRM 972); Dr. Hollis will report his assay performance based on this SRM.

Plasma EPA, DHA and total n-6 fatty acids will be assayed in the laboratory of proposed Collaborator Cdr. Dr. Joseph Hibbeln at the Laboratory of Membrane Biophysics and Biochemistry (LMBB), NIAAA, NIH. EPA and DHA will be quantified using a method developed at LMBB and detailed elsewhere[82, 83]. This high-throughput method employs fast gas chromatography and robotic transesterification to achieve fatty acid methyl ester (FAME) resolution at high accuracy and efficiency, allowing rapid separation and quantification of fatty acids. CVs are <10% for all plasma fatty acids.

8) Enhanced follow-up procedures.

We will institute enhanced follow-up procedures for those with elevated PHQ-8 scores[39, 59] in order to provide further assurance of participant safety. We will contact participants with elevated PHQ-8 scores (≥10 algorithm cutoff)132, 136 at baseline and follow-up (6.2.c.) by sending mailed letters, where there is no self-report by the participant of both recent diagnosis and treatment of depression on the questionnaire or an indication of such from the CMS data. Among all participants who score PHQ-8 ≥15, we will send these same letters, regardless of recent self-reported diagnosis or treatment for depression. A key goal is to ensure that participants are educated about the need to discuss their mood with their local providers and, thus, initiate a path for ongoing evaluation and/or treatment as necessary; thus, among participants who are randomized and continue in the study, we will only send these letters when participants first report above-threshold scores. As part of the VITAL informed consent procedure, participants will already have been notified that study investigators may need to contact them directly with regard to development of endpoints and also to obtain releases to contact their PCPs. VITAL-DEP will fund the effort of a research assistant who will assist the PI by coordinating with the Division to obtain contact information of persons with high PHQ scores, working with data programmers to send out the letters, and performing data tracking of the letters, as well as comments, questions or responses from participants in response to the letters.

9) Data management.

Because participants will be followed solely by mail and telephone, the computing system is a critical feature of effective follow-up. This system, which was developed and fine-tuned in our previous trials, tracks each participant's stage in the study and level of participation. It automatically generates letters, questionnaires, and phone call reminders at the appropriate times. Names, addresses, telephone numbers, participation status, and processing information are kept up to date, and data from questionnaires, letters, and phone calls are entered into the study database. When talking to a participant to follow-up on elevated PHQ scores (see as above), study personnel need ready access to identifying information, participation level, and the content of previous study-related telephone calls. However, it is also critical that these data be available only to authorized staff members. Our existing computer and security systems, which balance these considerations, will be used in VITAL.

Questionnaire data will be optically scanned into the computer. The relevant software—TELEform and Alchemy (Cardiff Software)—has been successfully used for several years in our studies. Out-of-range, internally inconsistent, and unclear data are reviewed by a verifier who corrects misread variables. Forms that cannot be scanned, and name and address changes, are entered using traditional double-entry procedures. All data undergo additional within-form and across-time checks to verify accuracy. The database will be maintained on a UNIX server. All data files will be backed up nightly, ensuring at least two current copies at all times. Each month, a set of data files will be taken off-site for long-term storage.

VI. BIOSTATISTICAL ANALYSIS

PRIMARY AIMS: Incident and recurrent depression in the full cohort.
Analyses of treatment effects will be based on the intent-to-treat principle.

First, to ensure that balance is achieved by the randomization, baseline characteristics (e.g., age, gender, race/ethnicity, physical activity, medical conditions, vitamin D and ω-3 intakes) will be compared by randomized groups using 2-sample t or Wilcoxon rank sum tests for continuous variables and χ^2 statistics for categorical variables.

Next, we will examine the main effects of intention-to-treat with vitamin D_3 or with fish oil. Kaplan-Meier survival curves will be used to determine cumulative depression incidence and recurrence for each treatment group and its corresponding placebo group; the log-rank test will be used to compare the curves of agent vs. placebo. We will use the Cox proportional hazards model to estimate the hazard ratios (HRs) and confidence intervals (CIs) for each intervention using indicators for treatment and controlling for design variables (the other intervention, age, and gender)[85]. Participants will be followed until the occurrence of the depression endpoint, death, loss to follow-up, or the end of the trial, whichever comes first. We will test the proportionality assumption (i.e., that of non-changing hazards ratios over time) both analytically and graphically. All analyses will be conducted with SAS version 9.1 (SAS Institute, Cary, NC), and a 2-sided test with α=0.05 will be used.

Finally, given potential concerns of participant non-adherence, drop-out, or case misclassification, additional analyses will be carried out. For example, we will address effects of compliance by censoring follow-up when a participant reports taking less than two-thirds of study medications over the previous year. In addition, because CTSC participants will have medical histories and physicals, cognitive exams and psychiatric interviews, we can directly observe[86] the extent to which outcome misclassification (which can be of unknown direction[87, 88]) occurs among medically-ill[89, 90] or cognitively-impaired persons. We can then correct estimates of the treatment effects and CIs in the full VITAL cohort using sensitivity analyses[86, 91].

PRIMARY AIMS: Longitudinal change in depression scores in the full cohort.

The primary analysis will examine the main effects of randomized vitamin D_3 or fish oil treatments on depression scores (PHQ-8) over the 5-year follow-up period. We will use a mixed-effects model for the four measures (years 0, 1, 3, and 5), including fixed effects for treatment, time and interaction between treatment and time, that accounts for the correlations between repeated measures; we will estimate the mean differences and 95% CIs. In secondary analyses, we will account for potential impact of initiation of antidepressants during follow-up. For example, if an agent reduces depressive symptoms, then those receiving placebo may be more likely to initiate antidepressants, which could lead to more conservative estimates of main effects on mood.

Analysis plan for categorical and continuous depression outcomes in the CTSC sub-cohort. As for our primary aim analyses, we will use survival methods to test whether there are significant differences in risk of the composite depression endpoint in the high-risk group, and of MDD in the subsyndromal group. For continuous PHQ-8 scores, we will use a mixed-effects model, including the two PHQ-8 measurements as the dependent variables and fixed effects for CTSC sites, treatment, time, and interaction between treatment and time, while accounting for the correlation between repeated measures in the same participant. We will estimate 95% CIs and P values for the two intervention main effects for change in depression scores between baseline and 2 years for each group. Given higher participant burden of in-person assessments, the CTSC sub-cohort may be slightly more affected by loss-to-follow-up than the full cohort. Thus, if follow-up is less than complete, we will conduct sensitivity analyses to estimate the effect under intention-to-treat[92, 93].

Analysis plan for nested case-control study of plasma levels of 25(OH)D and EPA+DHA. Circulating 25(OH)D is used as a reliable surrogate of vitamin D status[94, 95]. We will test the relative risk of having deficient plasma 25(OH)D levels (<50 nmol/L, or 20 ng/mL)[95-97] among cases compared to controls; deficiency prevalence is

~35-40%[98]. Using interaction terms, we will address whether response to treatment agent is modified by baseline levels of 25(OH)D (deficient vs. sufficient) or EPA+DHA (above vs. below median). We will also explore associations of low baseline plasma ω-3:ω-6 ratios with depression.

Analysis plan for effect modification and approach to exploratory analyses. With multiplicative interaction terms, we will study whether treatment effects for each intervention differ by the other intervention; African-American race, compared to Whites (for D_3); age; gender; baseline vitamin D and ω-3 intake (above vs. below median); medical comorbidity[89, 90, 99]; and geographic region/latitude and physical activity (for D_3). Parameters will be estimated with the Proc Mixed procedure of SAS, using a 2-sided test with α=0.05.

Power Calculations.

Our calculations show high statistical power for testing of all Primary Aims. All power calculations assume 80% compliance with the study agents, use a Stata (Stata Corporation, College Station, TX) program developed for multi-arm clinical trial designs[100, 101], and are based on the log-rank test and adjusted appropriately for design features, such as arbitrary time-to-event distribution, nonproportional hazards, non-uniform rates of entry, loss to follow-up, and treatment changes from allocated treatment[100].

Rationale for estimates of lifetime and current depression prevalence.
As power calculations of incidence and recurrence of depression will necessarily depend on lifetime and current prevalence of depression, we carefully reviewed the literature to arrive at age-, ethnicity- and gender-informed estimates of prevalence in our target population.

Lifetime prevalence of depressive disorders among men aged 60+ and women aged 65+ will determine the numbers of participants eligible for incidence and recurrence. Data from the NCS-R indicated 11.9% lifetime prevalence of depressive disorders[102]. However, gender-specific data from the Cache County study[103] report slightly higher lifetime prevalence among healthy, US elders (20.4% in women; 9.6% in men). One study reported slightly lower lifetime prevalence (6.3%) of depressive disorders among older blacks, compared to whites, but no difference by gender among blacks[14, 104].

Current prevalence of late-life depression was estimated at 13.34% in a meta-analysis [105]; there is little data directly comparing whites and minorities[14, 104, 106]. However, Blazer et al.[106] found no differences by race in the 9% current prevalence in the EPESE study. Thus, we used gender-specific estimates of lifetime prevalence[103], and the current prevalence from Blazer et al.[106] In other research involving large cohorts, we observed a history of any depression or antidepressant use among 8% of men aged 65+ in the Physicians' Health Study[107], and in the Nurses' Health Study, women aged 65+ had lifetime prevalence of depression or antidepressant use of 19.2% and current prevalence of 9.9% – supporting our estimates for VITAL. Alternative calculations show similarly high power even with a lower number of cases (e.g., 85% power for RR=0.80 when the number eligible for recurrence=2,200).

Rationale for estimates of depression incidence and recurrence rates.
Incidence rates (per 1000 person-years [p-y]) for combined depressive symptoms and syndromes were 19.3 (23.4 and 14.7 in women and men) in Luijendijk et al.[41] – very similar to those reported in the Cache County[108] and Goteborg[49] studies. Rates are not available by race/ethnicity. We used the slightly more conservative rates from Luijendijk et al[41].

The rates reported by Luijendijk and colleagues[41] are the only available directly estimated recurrence rates (i.e., as a function of person-time at risk) for late-life depression among community-dwelling participants. This group reported a recurrence rate of 65.6/1000 p-y for combined depression; this rate translates to ~30%

recurrence over 5 years, and thus is comparable to recurrence reported in smaller outpatient samples of adults[109-111]. We applied these gender-specific rates[41].

Table 2. Power for effects of a single agent on incident depression in VITAL, over 5 years of follow-up

RR†	Total	Women	Men	Non-Hispanic White	Minority	African-American
	15,470 ‡	7,244 ‡	8,226 ‡	10,071 ‡	5,399 ‡	3,868 ‡
0.90	52.6%	33.5%	24.9%	37.3%	22.3%	17.2%
0.85	86.7%	64.3%	49.5%	69.9%	44.3%	33.6%
0.80	98.6%	88.1%	74.8%	91.8%	68.9%	54.6%
0.75	>99.9%	97.8%	91.5%	98.9%	87.4%	74.8%
0.70	>99.9%	99.8%	98.1%	>99.9%	96.5%	89.1%
0.65	>99.9%	>99.9%	99.8%	>99.9%	99.4%	96.5%
0.60	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	99.2%

†Expected RR; ‡ Expected total number of eligible participants.

Table 3. Power for effects of a single agent on recurrent depression in VITAL, over 5 years of follow-up

RR†	Total	Women	Men	Non-Hispanic White	Minority	African-American
	2,730 ‡	1,856 ‡	874 ‡	1,777 ‡	953 ‡	683 ‡
0.90	38.2%	30.8%	12.7%	26.7%	16.4%	12.9%
0.85	70.9%	59.6%	23.5%	52.6%	31.6%	24.0%
0.80	92.1%	84.1%	38.5%	77.7%	51.3%	39.2%
0.75	98.9%	96.1%	55.7%	92.9%	70.9%	56.5%
0.70	>99.9%	99.5%	72.2%	98.6%	85.9%	72.9%
0.65	>99.9%	>99.9%	85.2%	99.8%	94.7%	85.6%
0.60	>99.9%	>99.9%	93.4%	>99.9%	98.5%	93.6%

†Expected RR; ‡ Expected total number of eligible participants.

Power calculations in the CTSC sub-cohort.
For depression prevention among high-risk participants, eligible persons are those without non-anxiety Axis I history, including dementia[112], or with past depression in remission for at least one year[79]. Of an estimated 855 eligible, high-risk people will comprise ~60% (n=513)[113]. High depression rates have been observed with key risk factors[114, 115]: e.g., Robinson et al.[115] found a 22.4% 1-year depression incidence in the placebo group of a prevention RCT among elders following acute stroke. Power was based on an expected 2-year incidence of 25%[38] in the placebo group. Of note, investigators have achieved RR reductions of 60% (i.e., an RR of 0.4) in prevention trials among high-risk persons[79]. We will have 80% and >95% power to detect RRs for a single agent of 0.6 and 0.5, respectively.

For MDD prevention among participants with subsyndromal symptoms, we considered the reported 21.3% current prevalence of subsyndromal depression among persons aged 65+ years[113]. Subsyndromal depression has been found among 13% of blacks and 28% of whites[116]. Thus, persons with subsyndromal symptoms will likely comprise 23% (n=196) of eligibles. One group[117] recently observed an 18-month MDD incidence of 25% among primary care adults with subsyndromal symptoms. Power was based on a 2-year risk of 35% in the placebo group; we will have 80% and >90% power to detect respective RRs of 0.5 and 0.4. If 2-year risk is higher (e.g., 45%), there will be 80% and >90% power to detect respective RRs of 0.6 and 0.5.

Rationale for power calculations in the nested case-control study. Using the most conservative incidence and recurrence rate estimates for depressive syndrome[41], we calculated the expected number of cases (n~900) – or ~500 with blood samples. To enhance power, cases will be matched 2:1 with controls on 5-year age group, gender, follow-up time and season of blood draw. We assumed 35 or 40% prevalence of vitamin D deficiency among controls[98]; for ω-3, we based power on low levels (bottom 25% or 33% of the control distribution). We

will have ≥80% power to detect RR=1.4 and >90% power to detect RR=1.5. A recent study[118] reported odds ratios for mood disorder of 2.6 for 25(OH)D=10-19.9 ng/mL, and 11.7 for 25(OH)D <10/ng/mL.

Power for additive and synergistic effects of the agents. Assuming a 2-sided α of 0.05, we calculated power of single agent effects ranging from 0.90 to 0.75, and RRs for interactions from 1.00 (i.e., additive) to 0.60. If both agents are effective, but act independently, power tends to decrease, due to a smaller number of events. If the agents interact, power will be affected by the extent of the interaction. We will have ≥80% power to detect important interactions (e.g., additional risk reduction of ≥30% for single agent RRs from 0.90 to 0.75).

Power for continuous outcomes[119, 120]. We used the SD of change in PHQ scores from two 1-year-apart assessments in a sample of non-depressed adults[59] and calculated power to detect a 25% difference – a clinically meaningful difference – compared to the mean of non-depressed persons at baseline[59]. We will have >99% power for Primary Aims and detecting differences by vitamin D3 among African-Americans. Mean differences may be greater among the higher-risk CTSC samples; we will have >99% power to detect a 30% difference in the high-risk group, and 90% power to detect a 30% difference among subsyndromal participants.

VII. RISKS AND DISCOMFORTS

There is the possibility of social/psychological risk that could result from inadvertent disclosure of confidential information from the questionnaires or blood tests. However, we have many safeguards in place to avoid this possibility, and we have never had an inadvertent breach of confidentiality in any of our trials.

The potential risk of disclosure of confidential information is guarded against by maintaining completed questionnaires and blood test results in locked offices accessible by authorized personnel only. In questionnaire data files, participants are identified only by study ID. Subject identifiers are stored in separate computer files with password protection, and results will be presented only in the aggregate. In addition, employees involved with the proposed study will be asked to sign a form agreeing not to disclose any information to which they might have access, regardless of their personal perception about its confidentiality. Each employee of the study who has access to study data or has contact with subjects participates in an institutional (Brigham and Women‘s Hospital) human subjects educational program, which consists of reviewing regulatory and informational documents pertaining to human subjects research; passing a test on ethical principles and regulations governing human subjects research; and signing a statement of commitment to the protection of human subjects. Finally, all such employees are required to participate in HIPAA training.

VIII. POTENTIAL BENEFITS

For the majority of participants, there will be few direct benefits from participating in this primary prevention study other than the awareness of being involved in a large endeavor to answer relevant and timely questions regarding the possible benefit of vitamin D and fish oil.

During the trial itself, we will receive inquiries from the participants regarding both specific and general health concerns. We will respond to each of those questions, primarily directing participants to published sources or recommending that they see their local health provider who is familiar with their medical history. In addition, participants may benefit from the letters sent to those reporting high levels of depressive symptoms. Many such persons might not otherwise be referred to their local providers for further evaluation and management of depression.

The purported health benefits of vitamin D and marine omega-3 fatty acids are receiving increasing attention in the medical literature and the popular press. Sales of vitamin D supplements and omega-3 fatty acid

supplements at U.S. stores have increased substantially in recent years. However, definitive data on health benefits and risks of these agents are lacking. Findings from this large clinical trial will clarify the role of vitamin D and marine omega-3 fatty acid supplements in the prevention of depression will help guide individual decisions, clinical recommendations, and public health guidelines.

IX. MONITORING QUALITY ASSURANCE

A. SAFETY MONITORING

An independent Data and Safety Monitoring Board (DSMB) will be assembled, consisting of experts in clinical trials, epidemiology, biostatistics, relevant clinical areas of cancer and CVD, cognitive function and NIH representatives. The Physicians' Health Study, the Women's Health Study, and the Women's Antioxidant and Folic Acid Cardiovascular Study (the main trials as well as ancillary outcome studies) have been monitored by the same DSMB since their inception. As two of these trials have ended and the third is in its last years, we will ask our DSMB members if they would be willing to also monitor VITAL. If they are not able to do so, we will consult with them in assembling a new DSMB. Current VITAL DSMB members are Drs. Lawrence S. Cohen, Theodore Colton, Mark A. Espeland, I. Craig Henderson, Alice H. Lichtenstein, Rebecca A. Silliman, and Nanette Wenger (chair). Ex officio members are Drs. Josephine Boyington (NHLBI), Rebecca B. Costello (ODS), Cindy D. Davis (NCI), Peter Greenwald (NCI), and Lawrence Fine (NHLBI). In addition, we will nominate experts in depression clinical trials and psychiatric outcome measurement to the VITAL DSMB. The DSMB Chair has strongly endorsed the importance of such experts on the DSMB, and their presence will ensure a high level of acumen for monitoring differences in depression by treatment arm.

The VITAL Data and Safety Monitoring Board (DSMB) will be charged with ensuring that the safety of participants is protected and that the scientific goals of the study are being met. The VITAL DSMB will include psychiatric expertise and will monitor differences by treatment arm of ancillary study outcomes, including depression, and will be empowered to terminate the trial based on evidence of substantial harm or benefit. To support those purposes, the DSMB will review any proposed amendments to the study protocol, examine the progress of the trial and the unblinded data on study endpoints, perform expedited review of all serious adverse events (i.e., events meeting the FDA definition of Serious Adverse Events, such as any fatal event including suicide, immediately life-threatening event, or permanently or substantially disabling event), perform ongoing monitoring of drop-outs and non-serious adverse events, determine whether study procedures should be changed or the study should be halted for reasons related to the safety of participants, and perform periodic review of the completeness and validity of data to be used for analysis of safety and efficacy. The DSMB will also ensure participant privacy and research data confidentiality.

The DSMB will annually examine the progress of the trial and the unblinded data on study endpoints and possible adverse effects to recommend continuation, alteration of study design, or early termination, as appropriate. Interim trial results will be assessed with the Haybittle-Peto rule, adjusting for multiple looks. In this method, interim results are compared to a z-score of 3 standard deviations (p=0.0027) throughout the trial. The final results may then be interpreted as having close to nominal significance levels. This rule appropriately requires very strong evidence for early stopping, is more conservative than the Pocock and O'Brien-Fleming rules and the alpha-spending function, and can be conducted at convenient times without inducing statistical complexity. The monitoring rules[121, 122] will serve solely as guidelines in decisions regarding continuation or stopping of treatment arms. All decisions will be made after examining the totality of evidence, including other trial data, on these agents.

B. MONITORING OF DATA

Redundancies will be built into the data processing systems to insure accurate recording of data and proper follow-up. All research forms will be scanned in and the data read by a character recognition software program

(Teleform). Out-of-range, internally inconsistent, and unclear data will be reviewed by a verifier who will edit misread variables. Forms that cannot be scanned, and name and address changes, will be entered using traditional double-entry procedures. All data will undergo additional within-form and across-time checks to verify accuracy. Following data entry, all questionnaire responses that require additional follow-up for missing data, participant comments on the form or for endpoint validation will be manually reviewed to insure correct processing and accurate follow-up. Address changes received from the post office or from participants will be manually keyed by data entry personnel and the resultant files compared and verified.

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