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

Christine M. Albert, M.D., M.P.H.

PROTOCOL TITLE

The VITAL Rhythm Study

FUNDING

Applied for National Institutes of Health (NIH) funding

VERSION DATE

October 15, 2012

SPECIFIC AIMS

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

Primary aims:

1. To test whether EPA+DHA supplementation influences risk of AF in a general population of men and women without prior cardiovascular disease.
2. To test whether vitamin D3 supplementation influences risk of AF in a general population of men and women without prior cardiovascular disease.

Secondary aim:

1. To examine the effect of vitamin D3 or EPA+DHA supplementation on electrocardiographic parameters to further understanding regarding mechanisms underlying associations with arrhythmic endpoints.

Tertiary aims:

1. To explore whether the effect of vitamin D3 or EPA+DHA supplementation on AF risk varies by (a) baseline blood levels of these nutrients and by (b) race/skin pigmentation (for vitamin D3).
2. To explore whether EPA+DHA supplementation or vitamin D3 supplementation reduces sudden arrhythmic death risk as compared to other causes of cardiovascular death.

BACKGROUND AND SIGNIFICANCE

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

Heart rhythm disorders are major causes of mortality and morbidity in United States. Atrial fibrillation (AF) is the most common heart rhythm disturbance and the prevalence is exponentially growing. An estimated 5.1 million people are diagnosed with AF in the United States at present, and this number is expected to rise to 7.5 million by 2020 and to 12.1 million by 2050. The clinical consequences of AF are considerable and include thromboembolic stroke, congestive heart failure (CHF), cognitive dysfunction, increased mortality, and a lower quality of life. Although AF often develops in patients with risk factors for cardiovascular disease (CVD), many individuals do not develop CVD preceding their AF diagnosis. Unfortunately, treatment of established AF is associated with limited long-term success rates and significant risks. Even when treatment is apparently successful, AF may continue undetected and the risk of stroke may never be eliminated. Therefore, substantial reductions in morbidity and mortality from AF will require the development of primary preventive interventions that can be applied to broad populations.

Omega-3 fatty acids have been documented to influence the electrical properties of the myocardium in experimental models and influence the propensity for atrial and ventricular arrhythmias in humans. There is a substantial body of evidence from observational studies suggests that increasing intake of n-3 fatty acids may lower risk of ventricular arrhythmias and SCD; whereas the observational data regarding atrial arrhythmias is mixed, with some studies suggesting benefit, others neutrality, and others raising the possibility of increased risk. Small secondary prevention randomized trials have demonstrated reductions in AF risk, while others have not. Although Vitamin D supplementation has been less well studied with respect to heart rhythm disorders, multiple observational studies have found associations between vitamin D deficiency and several AF risk factors including diabetes mellitus, CHF, and hypertension. However, paradoxically, recent preliminary data suggest that vitamin D deficiency may be associated with a lower risk of AF, and that vitamin D excess may be associated with an increased risk. Therefore, it will be important to investigate the impact of both of these widely-utilized agents on AF incidence in a randomized controlled trial setting.

The VITamin D and OmegA-3 TriaL (VITAL) is an ongoing randomized, double-blind, placebo-controlled, 2x2 factorial NIH-funded trial testing omega-3 fatty acids (Omacor® 840 mg eicosapentaenoic acid [EPA]+ docosahexaenoic acid [DHA]) and vitamin D_3 (2,000 IU/day cholecalciferol) in the primary prevention of cancer and CVD. The trial provides a unique opportunity to evaluate the impact of these primary preventive interventions on AF incidence among 20,000 men (aged 50+ years) and women (aged 55+ years) apparently healthy without pre-existing CVD. Benefits and risks with respect to AF incidence have been postulated for both of these agents as described above, but results are inconclusive. The purpose of this ancillary study is to ascertain and adjudicate AF outcomes for the primary aim of testing whether omega-3 fatty acid and/or vitamin D supplementation influence AF risk in the general population. In addition, we also plan to examine how these agents might impact intermediate phenotypes for heart rhythm disorders (electrocardiographic parameters), as well as explore effects on arrhythmic death and whether baseline blood levels and/or race modify treatment effects.

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."

Atrial fibrillation and sudden cardiac death assessments, as well as plasma analyses, will be conducted on the entire VITAL Study (Protocol: 2009-P-001217) population (n=20,000), and ECG analyses will be limited to the Clinical and Translational Science Center (CTSC) sub-cohort of 1000 VITAL participants who live near the Boston area and agree to participate in a series of ancillary studies (Protocol: 2010-P-002331) in addition to the main trial.

We will ascertain AF events utilizing self-reports of physician diagnoses of AF received on annual questionnaires from study participants supplemented by outpatient and hospital visits for AF identified through CMS linkage. We will also ascertain additional information regarding AF diagnosis from supplementary questionnaires, and we will seek consent to review all inpatient and outpatient hospital records pertaining to AF diagnosis and evaluation. AF events will be confirmed by an endpoint committee composed of cardiologists, which will also make a determination on AF subtype and pattern. In year five, an intention-to-treat analysis examining the main effects of omega-3 fatty acids and vitamin D on incident AF will be performed to address the primary aims.

Electrocardiograms (ECGs) will be obtained at baseline and again after two years of treatment and follow-up among a sub-cohort of 1,000 patients being enrolled in VITAL at the CTSC. In years three and four, we will utilize these ECG data to evaluate whether treatment with omega-3 fatty acids and vitamin D_3 have significant effects on ECG measures of atrial and ventricular conduction, repolarization, and

autonomic function (i.e., resting heart rate, P-wave indices, PR interval, QRS duration, QT interval, and HRV). The ECGs will also be utilized to estimate the prevalence of asymptomatic persistent AF in our population not detected by our AF surveillance methods.

In year five, 25(OH) vitamin D and EPA/DHA levels from the parent VITAL Trial will be measured in previously-collected plasma specimens from an estimated 500 AF cases and a random cohort of 2000 participants using a nested case-cohort design to explore whether the effect of vitamin D3 or EPA+DHA supplementation on AF risk varies by the baseline blood levels of these nutrients. Throughout the five year grant period, we will also seek additional information necessary to classify deaths as sudden or arrhythmic in origin, and cardiac deaths will be reviewed by an endpoint committee of cardiologists. Also in year five, we will explore whether omega-3 fatty acids and/or vitamin D might have an effect on sudden and/or arrhythmic cardiac death.

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.

The primary study endpoint is the development of atrial fibrillation. AF will be assessed in two ways; self-reports via study participants and Centers for Medicare and Medicaid Services (CMS) data linkage. HIPAA- and IRB-certified researchers will obtain a list of participants who indicated that they have been diagnosed with AF during the course of the study. We will utilize the same follow-up procedures which have been successful in validating AF in other population-based cohorts, which include the Physician's Health Study I and II (Protocol 2003-P-000666), Nurses' Health Study, Women's Health Study, Women's Antioxidant Cardiovascular Study. These participants will then be sent a new HIPAA-compliant consent form for the release of their medical records along with a supplementary questionnaire regarding the details of their history of AF. We will initiate three mailed attempts consisting of a letter, two-page questionnaire, and a medical record release form to participants. In the event of no response, a fourth request letter and a brief version of our original two-page questionnaire will be mailed. If no response is received, one final attempt to contact the participants via telephone will be taken. We will also mail letters to the next-of-kin requesting permission to obtain medical records of deceased participants that have previously reported that they have been diagnosed with atrial fibrillation. If no response is received, we will follow up with a phone call. Only after signed consent has been provided will researchers obtain the medical records using the information provided on the consent form. AF events will be confirmed by an endpoint committee composed of cardiologists, which will also make a determination on AF subtype and pattern.

In addition to assessing self-reports of atrial fibrillation from study participants on annual questionnaires, we will also ascertain AF diagnoses (ICD-9 diagnosis code 427.31) by linking our data with the CMS database. CMS linkage is also being performed as part of the parent trial. Each year, we will obtain Medicare Data Files through ResDAC, a CMS contractor providing assistance to academic researchers. These data usually include diagnoses and procedure codes for all reimbursed services. Data use agreements delineate confidentiality requirements of the Privacy Act and data release policies. Social security number, date of birth, or Medicare ID (HIC) can identify participants. We will obtain MedPar Inpatient and Skilled Nursing Facility (inpatient stay records), outpatient visit data, home health visit data, non-institutional provider data, and Bene ID Conversion File. Death certificates and death records will also be reviewed for AF diagnoses.

Sudden cardiac death (SCD) is the secondary endpoint and will be assessed on all cardiac deaths and out-of-hospital deaths that occur without a clear non-cardiac underlying cause. We will utilize the same follow-up procedures which have been successful in validating SCD in other population-based cohorts, which include the Physician's Health Study I and II, Nurses' Health Study, Women's Health Study, Women's Antioxidant Cardiovascular Study, and Health Professional Follow-Up Study (Protocol 2003-P-000798) and the PRE-DETERMINE: Biologic Markers and MRI SCD Cohort Study (Protocol 2007-P-

000840). We will review previously-collected death information, including medical records, death certificates, autopsy/coroner reports, and correspondence from family members to determine if additional information is needed to validate sudden cardiac death. A letter and questionnaire will be mailed to the next-of-kin specifically asking for information that will allow the determination of the timing and mechanism of death. If the next-of-kin does not respond to the mailing, we will follow up via telephone. Sensitive phone interviews will be conducted for those participants who have died unexpectedly (without an imminently fatal condition) outside of the hospital with the next-of-kin and other potential witnesses regarding the details and circumstances surrounding the death. Since most arrhythmic deaths do not take place in a hospital setting, every attempt will made by the research assistants to obtain descriptions of the death from witnesses and/or detailed EMT or emergency room medical records. Sudden cardiac deaths will be confirmed by an endpoint committee composed of cardiologists and will utilize a combined sudden and/or arrhythmic death endpoint for analyses, which will include deaths fulfilling the definition of SCD (definite and probable) and/or arrhythmic death (definite and probable). Deaths that are classified as non-arrhythmic are excluded from the endpoint regardless of timing.

Electrocardiograms (ECGs) are currently being obtained at baseline among a sub-cohort of 1,000 patients being enrolled in VITAL at the CTSC, and as part of this protocol after two years of treatment and follow-up. Three ECG recordings will be collected per visit and stored for future analysis as well as Quality Assurance (QA) assessment at the EPICARE Center, Wake Forest University Baptist Medical Center, Winston-Salem, NC. Dr. Elsayed Soliman is the director of the center and will head this endeavor at EPICARE. Data will be sent with de-identified anonymous study numbers only, by mail or by secure electronic transfer. The first ECG, providing it passes quality control standards, will be the main ECG from which all measure will be taken. The two additional ECGs will be used for heart rate variability (HRV) that is averaged over the three ECGs. The recordings will be made with a GE MAC1200 machine, which offers digital recording of ECGs and direct data transmission. ECG technicians at the CTSC will be trained on standard ECG recording and certified. ECG data will be sent with de-identified anonymous study numbers only by mail or by secure electronic transfer. The digital ECGs will be stored in an electronic database at the VITAL ECG reading center at EPICARE in a Marquette measurement matrix by participant ID. This database will remain unaltered. Additionally, a second and third database will be created after technician editing of correct onset and offset of the waveforms. Monthly reports will be sent from the reading center to the CCC.

EPICARE will perform quality control checks, read, and code the study ECGs using standardized methods that have been developed by the center. The EPICARE ECG coding program will classify the ECG into Minnesota Code and Novacode categories. Minnesota ECG coding has significantly improved standardization of ECG measurements and enhanced the comparison of ECG findings from epidemiologic studies and clinical trials. In addition to the categorical classification of Minnesota Code, the ECG reading center will provide a large dataset that includes the durations and amplitudes of each segment of the ECG waveform in each lead. Standardized measurements of interests that may represent important intermediate phenotypes for AF or SCD will include heart rate (R-R interval), PR duration, P-wave indices (axis, amplitude, duration, and area), QRS duration and conduction defects, and QT interval. We will also examine two short-term time domain HRV indices: (1) the standard deviation of all filtered RR intervals over the length of the recording (SDNN), and (2) the root mean square of the difference of successive RRs (RMSSD). These measures are obtained from ten-second ECGs that are processed digitally in accordance with the current HRV guidelines. To have better repeatability, we will use the average of these measures in three consecutively-recorded ECGs.

Blood specimens that were previously collected on all willing subjects during the run-in phase of the parent trial will be sent to laboratories and analyzed in blinded fashion. Approximately 80% of participants (n=16,000) are expected to provide a sample. Fasting blood samples will also be collected during trial years two and four from a randomly-selected subset of 2,000 participants who previously provided baseline samples to assess compliance and changing trends in background fortification with vitamin D and marine omega-3 fatty acids. All cases and controls from a given cohort will be shipped in

the same batch and assayed in the same analytical run. Coefficients of variation will be measured by analyzing blinded quality control samples randomly distributed throughout the study samples. Plasma 25(OH) D will be measured using a radioimmunoassay (RIA). This assay (DiaSorin Corporation, Stillwater, NM) quantitates 25(OH) D2 and 25(OH) D3 equally, and has been in widespread use for nearly twenty years. The intra- and inter-assay variations are <10%. We will also be measuring fatty acid profiles using gas chromatography in the laboratory of Dr. William Harris. The coefficient of variation for EPA+DHA as a percent of total RBC fatty acids (our metric of primary interest) is 5.0% for a mean value of 10.9% (SD = 0.5%) and 5.3% for a mean value of 3.8% (SD = 0.2%). Because specimens will have been frozen at -170 ºC, we do not anticipate problems with degradation. For example, normal-range values and stability of EPA/DHA levels have been demonstrated in the Physicians' Health Study following long-term storage of more than fifteen years.

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.

The study does not involve treatment or diagnosis.

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.

Since there are no new interventions required for this ancillary study accept to collect ECGs and medical information on AF and SCD, the only possible risk involved in this study involves the potential social and psychological risks associated with the extremely unlikely inadvertent disclosure of confidential medical information.

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.

Not applicable for this ancillary study since no new intervention will be added to the study. Monitoring for safety will be performed as described under the parent VITAL Study (Protocol: 2009-P-001217) and Clinical and Translational Science Center (CTSC) (Protocol: 2010-P-002331).

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 are no foreseeable risks or discomforts to participants posed by this ancillary protocol.

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.

Direct benefit of participation is limited. However, we hope the information collected will help to increase medical knowledge about the life-threatening heart rhythm disturbances and new primary preventions.

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.

Potential participants will include all previously-enrolled participants in the VITAL Study. The gender distribution of the 20,000 participants in VITAL will be 50% male and 50% female—specifically, 10,000 men aged ≥50 and 10,000 women aged ≥55. Estimates of the race/ethnicity of the participants come from the pilot study, in which the source list of individuals to whom were mailing was enhanced with names identified as possible minorities. Based on the pilot results, approximately 40,000 willing and eligible participants were identified to enter the run-in, with at least 25% underrepresented minorities; 20,000 of these will be randomized into the trial, with the same proportion minority. Specifically, of the 20,000 randomized participants, the ethnic distribution is estimated to be 1,400 (7.5%) Hispanic and 18,600 (93%) non-Hispanic; with regard to race, 5000 (25%) African-American, 500 (2.5%) Asian, 400 (2%) American Indian, 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 CTSC sub-cohort is expected to have the same racial/ethnic composition as the overall VITAL cohort. No exclusions at the time of enrollment were made on minority status. The burdens and benefits of the study will be distributed evenly across participants.

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.

Because VITAL is not able to determine beforehand who on their mailing list is not able to speak English, it will not be possible to target these individuals with recruitment materials written in a different language. However, every effort will be made to accommodate those who speak a foreign language, particularly Spanish, by including Spanish-speaking individuals on our staff who may be able to assist participants with their questions and collect follow-up data verbally over the phone.

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.

Subjects will be recruited for the main VITamin D and OmegA-3 TriaL (VITAL) trial as outlined in Protocol: 2009-P-001217. Atrial fibrillation and sudden cardiac death assessments, as well as plasma

analyses, will be conducted on the entire VITAL Study (Protocol: 2009-P-001217) population (n=20,000), and ECG analyses will be limited to the Clinical and Translational Science Center (CTSC) sub-cohort of 1000 VITAL participants (Protocol: 2010-P-002331). No new subject recruitment will take place as part of this ancillary study.

To date, 6.3 million ethnically and racially-diverse people, including health professionals, AARP members, Essence subscribers, other professionals, college-educated individuals, and Black business professionals, were mailed a detailed description of VITAL's objectives and a brief questionnaire to determine initial willingness and eligibility. Currently, 83,129 individuals were found to be willing and eligible on this initial screen and have been sent a longer questionnaire with more detailed questions regarding eligibility along with a consent form. In brief, to be eligible for the trial, subjects must (1) be age ≥50 (men) or ≥55 (women); (2) have no history of cancer (except non-melanoma skin cancer), MI, stroke, transient ischemic attack, angina pectoris, coronary artery bypass graft, or percutaneous coronary intervention; (3) have no history of safety exclusions; (4) have no allergy to fish; (5) have no other serious illness that would preclude participation; (6) be willing to consume <800 IU of vitamin D and <1,200 mg/d of calcium from all supplemental sources combined; (8) be willing to forego fish oil supplements; and (9) have the ability to provide informed consent.

Of the 20,000 participants enrolled, 1,000 who live near the Boston metropolitan area and agree to participate in a series of ancillary studies will also be enrolled in the CTSC sub-cohort. In addition to fulfilling eligibility criteria for the main trial, CTSC participants must live within driving distance of the Boston CTSC and be able to provide informed consent for the CTSC evaluation. The CTSC sub-cohort is expected to reflect the diverse racial/ethnic composition of the VITAL study population and will be randomized equally into the four treatment groups created by the factorial design (1,000 overall; 250 participants in each of the 4 groups: vitamin D alone, omega-3 alone, both agents, or both placebos). CTSC participants will visit the CTSC sites for detailed health assessments prior to randomization and then again two years later.

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

Remuneration will not be offered as part of this ancillary study.

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.

All study participants have previously signed a consent form for their participation in the parent VITAL study and CTSC, if appropriate. A questionnaire will be mailed to the participants who report having AF on the main study questionnaires. Completion of the questionnaire will indicate informed consent for the information provided on the questionnaire. Because the questionnaire will be mailed, the participants will be given as much time as needed to determine if they will participate. Participants and next-of-kin will also be sent a new HIPAA-compliant medical record release form asking for permission to access medical records pertaining to the participant's diagnosis of AF and/or SCD. Contact information for the parent trial is included in this correspondence if questions should arise regarding the research or the consent process.

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.

For the parent VITAL trial, an independent Data and Safety Monitoring Board (DSMB) has been assembled, consisting of experts in clinical trials, epidemiology, biostatistics, relevant clinical areas of cancer, CVD, and other chronic diseases, and NIH representatives. The DSMB plans to add expertise in the subject areas of ancillary studies whenever such expertise is deemed lacking. The DSMB has reviewed all study material to ensure the scientific validity of the parent trial and ancillary studies and safety of participants. The DSMB will annually examine the progress of the VITAL trial and all ancillary studies, including the unblinded data on study endpoints and possible adverse effects. Following each review, the DSMB will 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 three 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 VITAL DSMB will be overseeing the safety of each of the ancillary studies, including the VITAL Rhythm Study, and will receive at least annual summaries of safety. These are the safety summaries that will be shared with the NIH Program Officer. Several members of the VITAL DSMB have adequate clinical expertise to review the data. Current DSMB members are Drs. Lawrence Cohen, Theodore Colton, I. Craig Henderson, Rebecca Silliman, Mark Espeland, Alice Lichtenstein, and Nanette Wenger (chair). Ex officio members are Drs. Cindy Davis (NCI), Peter Greenwald (NCI), Josephine Boyington (NHLBI), Rebecca Costello (ODS/NIH), and Lawrence Fine (NHLBI). Dr. Nanette K. Wenger, Professor of Medicine (Cardiology), serves as the DSMB chair and also its CVD/diabetes expert.

While these rules are intended for the primary endpoints of VITAL (primary prevention of cancer and CVD), the DSMB will also consider the VITAL Rhythm Study as major endpoint (i.e. AF and SCD cases) in assessing the overall balance of benefits and risks of the two agents. In addition, the monitoring rules will serve solely as guidelines in decisions regarding continuation or stopping of treatment arms. All decisions must 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 overall VITAL trial and ancillary studies; and the unblended 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.

As mentioned above, the VITAL DSMB has reviewed all study material to ensure the scientific validity of the parent trial and ancillary studies and safety of participants. The DSMB will annually examine the progress of the VITAL trial and all ancillary studies, including the unblinded data on study endpoints and possible adverse effects. Following each review, the DSMB will recommend continuation, alteration of study design, or early termination, as appropriate.

For both this ancillary study and the parent VITAL Study, 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 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.

The VITAL Study has also taken great care to insure that participants receive their randomly-assigned drugs. Upon receipt of drug shipments from the manufacturer, each of the four drug groups will be stored in segregated areas. A random sample of drugs bottles or calendar packs will be pulled from each drug group and blindly tested to insure that the packaged contents match the study label. At the time of packaging for shipment to individual participants, listings will be divided according to drug group assignment and only one group will be packaged at a time. The packaging area will be cleaned and cleared prior to packaging and shipment of the next drug group. If drug packages are returned by the postal service as undeliverable or declined by a participant, the contents of the package will be blindly tested as an additional level of quality control.

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.

Several measures will be taken to insure the confidentiality of collected data. All research records will be stored in locked files in a secure facility at the Division of Preventive Medicine at BWH. Access to personally-identifiable information will be limited solely to the researchers responsible for obtaining medical records and confirming study endpoints. The endpoint committee will review these files, and the results of the endpoint data review will be stored according to the study ID.
Subject identifiers that are stored in computer files have password protection, and results will be presented only in the aggregate. 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.

We plan to retrieve additional data on AF diagnosis codes by linking the participants with Medicare claims inpatient and outpatient databases from the Centers for Medicaid and Medicare Services (CMS). Medicare is a US federal health insurance program that reimburses in-patient costs for most citizens and permanent residents aged ≥65 years. On an annual basis, we will obtain identifiable (Medicare) Data Files through ResDAC (www.resdac.unm.edu/Index.asp), which is a CMS contractor that provides free assistance to academic and non-profit researchers interested in using Medicare or Medicaid data. The data use agreement (DUA) delineates the confidentiality requirements of the Privacy Act and data release policies and procedures. Participants can be identified via their social security number and date of birth or through their Medicare ID (HIC). We will carefully adhere to the DUA, the confidentiality requirements of the Privacy Act, and data release policies and procedures. The VITAL data coordinating center will address the issues regarding ensuring data integrity, security, and confidentiality through a System Security Plan to the NHLBI. All VITAL coordinating center staff will sign a confidentiality agreement, as well as attend HIPAA and IT security training. The CMS data will be securely stored at the Division of Preventive Medicine, with access to the building controlled by key card, with security personnel monitoring the entrance. The original media on which the CMS data are supplied will be stored in a locked cabinet. Clinical coordinating center passwords will be required to conform to our password policy. Log-on access to the database will be password protected. Individually identifiable or deducible data will not be transmitted by unsecured telecommunications. The data will not be physically moved or transmitted from the clinical coordinating center without written approval from CMS. At the conclusion of the study, or by the date of retention identified in the DUA, a CMS "Certification of Destruction" certifying the proper destruction of all data obtained will be sent to CMS. These data files will be obtained through independent funding and will be available to the VITAL parent trial and all VITAL ancillary studies.

Electrocardiograms (ECGs) will be collected under the parent trial and as part of this protocol after two years of treatment and follow-up and sent to the VITAL Rhythm ECG core lab, EPICARE, for storage and future analyses. ECG technicians at the CTSC will be trained on standard ECG recording and certified. ECG data will be sent with de-identified anonymous study numbers only by mail or by secure electronic transfer. The digital ECGs will be stored in an electronic database at the VITAL ECG reading center at EPICARE in a Marquette measurement matrix by participant ID. This database will remain unaltered.

Blood samples will also be collected under the parent trial and sent the Blood Core laboratory for storage and futures analyses. Blood that will be sent for analysis will only be labeled with a designated unique bar code. The secure files containing the link between the study ID number and the identifying information required for the endpoint follow-up will be kept in a separate secure location. Authorized study staff who will be handling the blood samples will not have access to this link or any personally-identifying information or blood test results on patients. Therefore, it will be impossible for investigators or staff at BWH to trace to whom the sample belongs. The results of any analyses on these samples will only be for research purposes. Such research results are preliminary, inconclusive, and not necessarily valid for use by doctors in the management of patient's healthcare. Therefore, neither the site's Principal Investigator, nor the patient, will be informed of the results; the results will not be placed in the patient's medical record.

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.

The electrocardiogram (ECG) data will be stored for future analysis as well as for Quality Assurance (QA) assessment at the EPICARE Center, Wake Forest University Baptist Medical Center, Winston-Salem, NC. Dr. Elsayed Soliman is the director of the center and will head this endeavor at EPICARE. Data will be sent with de-identified anonymous study numbers only, by mail or by secure electronic transfer. A data storage agreement has been established with Wake Forest University Baptist Medical Center for ECG analysis and storage.

Only authorized researchers participating in the study will need to have access and be principally involved in all biomarker analysis. The laboratories that we are planning to utilize for theses analyses will not be used until year three and four. At that time, all authorized researchers participating in the study analysis will be required to complete a Letter of Agreement for Transfer of Non-Identifiable Samples and any other necessary forms to be in full compliance with the IRB regulations.

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.

Electrocardiogram data will only be stored at the EPICARE Center. IRB approval from the EPICARE Center to receive and store the ECG data has been attached.

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.

N/A