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

Michal L. Melamed, MD, MHS, Overall Principal Investigator (Albert Einstein College of Medicine)
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PROTOCOL TITLE

Effects of Vitamin D and Fish Oil on the Kidney in Hypertensives

FUNDING

National Institutes of Health R01 DK102952-01

VERSION DATE

August 28, 2015

SPECIFIC AIMS

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

To test whether cholecalciferol (vitamin D_3, 2000 IU per day) and/or marine omega-3 fatty acids (ω-3 FA, eicosapentaenoic acid plus docosahexaenoic acid, 1 gm per day) prevent the development and progression of kidney disease in individuals with hypertension, compared with placebo.

BACKGROUND AND SIGNIFICANCE

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

Chronic kidney disease (CKD) is a common and morbid complication of hypertension. Preventing the development and progression of CKD is a critical goal for improving long-term health outcomes of the hypertensive population and for reducing the overall burden of kidney disease in the United States. Therefore, there is an urgent need for additional, complementary interventions to prevent and treat CKD associated with hypertension. This need is greatest among older adults because hypertension and kidney disease are highly prevalent among older adults and kidney disease is among the strongest risk factors for mortality in this group. Vitamin D and omega-3 fatty acids (ω-3 FA) are two of the most promising interventions for CKD prevention and treatment. Because cholecalciferol and ω-3 FA are relatively safe, inexpensive, and widely available, they may offer opportunity to substantially reduce the burden of CKD in large populations. Prior to widespread implementation, however, these hypothesized benefits should be rigorously tested in well-powered clinical trials.

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."

This protocol summary describes an ancillary study to the NIH-funded ***VIT***amin D and Omeg***A***-3 Tria***L*** (***VITAL***), an NIH-funded randomized, double-blind, placebo-controlled trial. The overall goal of the ancillary study is to determine whether cholecaliferol and/or ω-3 FA supplementation prevents the development and progression of kidney disease in participants with baseline hypertension and no diabetes mellitus.

All participants in our ancillary study must be existing participants in the parent VITAL study. The parent VITAL study is being conducted among 25,875 healthy participants. The VITAL study population is restricted to older individuals (men ages ≥ 50 years, women ages ≥ 55 years), because rates of chronic disease (including CVD, cancer, and kidney disease) increase substantially with age. VITAL will exclude persons with clinically apparent CVD or cancer (except non-melanoma skin cancer), because it is a trial for the primary prevention of these conditions. Other eligibility criteria are focused largely on safety. VITAL oversampled for participants of black and Hispanic race/ethnicity.

To initiate our VITAL Hypertensive Kidney ancillary study, we will identify and recruit a sub-cohort of 4,000 VITAL participants with hypertension at baseline. Among this group, we will test whether the randomly assigned VITAL cholecalciferol and ω-3 FA interventions reduce the loss of estimated glomerular filtration rate (GFR) or the prevalence of albuminuria at year 4.

We will collect blood samples after 4 years of therapy to estimate GFR, comparing this to GFR estimated from blood samples at pre-randomization baseline collected by the parent VITAL trial. We will also collect urine samples at year 4 post-randomization.

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.

For the VITAL Hypertensive Kidney ancillary study described herein, we will collect questionnaire data, urine samples, and blood samples. Questionnaires will address hypertension diagnosis, hypertension history, history of kidney disease, and medication use related to hypertension and kidney disease. Blood samples will be collected after 4 years of therapy at local medical providers or via a phlebotomy service at the participant's home and submitted via mail. Urine samples will be collected and home and submitted via mail after 4 years of therapy.

There is another VITAL ancillary study which is currently funded to collect bloods on 400 participants at year 4. It is important to minimize participant burden and eliminate the possibility that a subject would be asked to provide 2 blood samples in the same follow-up period. Thus, we would like to clarify that, in the event that a participant in the VITAL Hypertension Kidney ancillary study is also selected for the subgroup of N=400 that will be asked to provide a blood sample at 4 years for the other ancillary study, the VITAL Hypertensive Kidney ancillary study will NOT collect a separate/additional 4 year follow-up sample from that participant. We will only send the kidney questionnaire to participants not in the N=400 subgroup.

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.

Not applicable.

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.

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.

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.

This ancillary study is not administering any treatments. All treatment monitoring occurs through the parent VITAL study.

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.

The blood draw may cause pain at the place where the needle is inserted, bruising, a hematoma (collection of blood underneath the skin), or infection at the place where the needle is inserted. Some people feel anxious with blood draws and may faint. There is also the possibility of social/psychological risk that could result from inadvertent disclosure of confidential information from the questionnaires or blood tests.

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 no direct benefits from participating in this 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 on hypertensive kidney disease.

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 VITAL Hypertensive Kidney study will reflect the hypertensive parent VITAL study population. The parent VITAL study is being conducted among almost 26,000 apparently healthy participants. The VITAL Hypertensive Kidney study population is restricted to older individuals (men ages ≥ 60 years, women ages ≥ 65 years), because rates of kidney disease increase substantially with age. VITAL oversampled for participants of black and Hispanic race/ethnicity, therefore, we expect the VITAL Hypertensive Kidney study will also have an adequate representation of participants of black and Hispanic race/ethnicity.

The VITAL Hypertensive Kidney study will enroll approximately 4000 prospective VITAL participants who indicate they have a diagnosis of hypertension, and who are willing to participate in the VITAL Hypertensive Kidney ancillary study.

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 VITAL Hypertensive Kidney study will be conducted entirely by mail. Fluency in the English language is required for safe participation.

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.

Persons willing to participating in the parent VITAL trial will return their year 4 questionnaires. Those who respond “YES” to the question “Have you EVER been diagnosed as having high blood pressure?” on their baseline questionnaires and have a pre-randomization blood sample available and who indicated "YES" or "MAYBE" to the question "Are you willing to give a blood sample?" (in addition to meeting initial parent VITAL trial eligibility criteria) will be targeted for VITAL Hypertensive Kidney ancillary study recruitment. Participants will also have to have answered “NO” to “Have you EVER been diagnosed as having diabetes?” After the participants return their year 4 questionnaires we will send eligible patients a separate questionnaire including:

- Letter explaining the rationale for the VITAL Hypertensive Kidney ancillary study,
- Hypertensive Kidney ancillary study informed consent form,
- Hypertensive Kidney ancillary study questionnaire, and
- Self-addressed, pre-paid FedEx box for returning study materials.

The VITAL Hypertensive Kidney ancillary study letter will outline what participation in the VITAL Hypertensive Kidney ancillary study would entail and will provide sources for further information

on relevant scientific issues. It will explain that participation in the ancillary study is optional and that it will not affect participation in the parent VITAL trial.

The VITAL Hypertensive Kidney ancillary study questionnaire will include items which clarify the self-reported diagnosis of hypertension and further define hypertension and kidney disease history, including previous dialysis treatments. All persons will have the option to decline VITAL Hypertensive Kidney ancillary study participation by checking a single box on their initial contact letter and returning this by mail to the VITAL coordinating center, or by calling the toll-free VITAL telephone number.

All potential participants who return a valid VITAL Hypertensive Kidney ancillary study consent form and agree to blood draws will be enrolled in the VITAL Hypertensive Kidney ancillary study. In the consent form, participants will decide whether they want to get bloods drawn by their local physician or clinic or whether they want a phlebotomy service to come to their home to draw the bloods. Blood and urine collection kits will then be mailed to the participants. Follow-up telephone calls will be used to remind potential participants to complete blood and urine collections, if needed. The first 4,000 VITAL participants who return the informed consent form, the Hypertensive Kidney questionnaire and the bloods and urine will be enrolled in the VITAL Hypertensive Kidney ancillary study.

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

Participants will receive $50 for participation in this 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.

A VITAL Hypertensive Kidney consent form will be mailed to each potential participant as part of their initial VITAL Hypertensive Kidney ancillary study packet.

All persons will have the option to decline VITAL Hypertensive Kidney ancillary study participation by checking a single box on their initial contact letter and returning this by mail to the VITAL coordinating center, or by calling the toll-free VITAL telephone number.

The initial contact letter and consent form will encourage participants to ask questions or address concerns by calling the toll-free VITAL telephone number to speak with study staff in person. Willing potential participants will return the final signature page of their consent forms to the VITAL coordinating center by mail. The consent form has been formatted so that all information about the study appears on pages 1 through 8 of the form, and the final page, page 9 contains the "Informed consent and authorization" section, which the participant is instructed to read and, if in agreement, to sign. This signature page (page 9 of the consent form) will be formatted in Teleform software which allows for the data on the form [signed OR not signed] and the image of the form to be captured via an optical scan process. Study staff will contact potential participants by telephone to clarify ambiguous or invalid consent forms.

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) has been assembled for the parent VITAL trial, consisting of experts in clinical trials, epidemiology, biostatistics, relevant clinical areas of cancer and CVD, and NIH representatives. If necessary, the DSMB will review adverse events related to VITAL ancillary studies, including VITAL Hypertensive Kidney.

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

All potential adverse events arising from parent VITAL study interventions will be reviewed by investigators leading the parent VITAL study.

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.

Because participants will be followed solely by mail, the VITAL computing system is a critical feature of effective recruiting and follow-up. This system, which was developed and fine-tuned in previous trials led by VITAL investigators, tracks each participant's stage in the study and level of participation. Computer systems allow access by study personnel to identify information while maintaining strict security. 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 the Women's Health Study and Physicians' Health Study. All data undergo additional within-form and across-time checks to verify accuracy; and are backed up nightly.

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. 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.

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.

Data will be sent from Partners investigators to the overall Principal Investigator of this ancillary study: Michal L. Melamed, MD, MHS, at the Albert Einstein College of Medicine (Bronx, NY). Data will include demographics, comorbidities, medication use, and adherence to study medications (all assessed by questionnaire); treatment assignments; and laboratory data generated by the parent VITAL study. Specimens will be sent from Partners investigators to a co-Investigator: Ian de Boer, MD, MS, at the University of Washington (Seattle, WA). Specimens will include urine and blood. The University of Washington will perform laboratory studies for this ancillary study including: serum creatinine, cystatin C and FGF-23 and urine albumin and creatinine levels. All biospecimens and data will be completely free of identifiers that could be used to link the specimens and data to individual subjects.

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 and data stored at the University of Washington and the Albert Einstein College of Medicine will be used only for the procedures described in the study protocol. Participants may withdraw their specimens and data at any time by request in writing to the VITAL coordinating

center. The ancillary study proposed herein will be submitted to the Albert Einstein College of Medicine IRB concurrent with submission to the Partner's IRB.

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.

Not applicable.