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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Scientific Information Request on Omega 3 Fatty Acids and Cardiovascular Disease – Update

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Scientific Information Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review of Omega 3 Fatty Acids and Cardiovascular Disease – Update, which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Programs. Access to published and unpublished pertinent scientific information will improve the quality of this review. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

DATES: Submission Deadline on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES:

Online submissions: http://effectivehealthcare.AHRQ.gov/index.cfm/submit-scientific-information-packets/. Please select the study for which you are submitting information from the list to upload your documents.
E-mail submissions: SIPS@epc-src.org.
Print submissions:
Mailing Address:
Portland VA Research Foundation
Scientific Resource Center
ATTN: Scientific Information Packet Coordinator
PO Box 69539
Portland, OR 97239

Shipping Address (FedEx, UPS, etc.):
Portland VA Research Foundation
Scientific Resource Center
ATTN: Scientific Information Packet Coordinator
3710 SW U.S. Veterans Hospital Road
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Portland, OR 97239

FOR FURTHER INFORMATION CONTACT:

Ryan McKenna, Telephone: 503-220-8262 ext. 58653 or Email: SIPS@epc-src.org.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Programs to complete a review of the evidence for Omega 3 Fatty Acids and Cardiovascular Disease – Update.

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on Omega 3 Fatty Acids and Cardiovascular Disease – Update, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at: http://effectivehealthcare.AHRQ.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2060

This notice is to notify the public that the EPC Program would find the following information on Omega 3 Fatty Acids and Cardiovascular Disease – Update helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number.
    - For completed studies that do not have results on ClinicalTrials.gov, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.

- A list of ongoing studies that your organization has sponsored for this indication. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute all Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution will be very beneficial to the EPC Program. The contents of all submissions will be made available to the public upon request. Materials submitted must be publicly available or can be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: http://effectivehealthcare.AHRQ.gov/index.cfm/join-the-email-list1/.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions. The entire research protocol, is available online at: http://effectivehealthcare.AHRQ.gov/search-for-

guides-reviews-and-reports/?pageaction=displayproduct&productID=2060

The Key Questions

1. What is the efficacy or association of n-3 Fatty Acids (FA) (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]EPA+DHA, docosapentaenoic acid [DPA], stearidonic acid [SDA], alpha-linolenic acid [ALA], or total n-3 Fatty Acids) exposures in reducing cardiovascular disease (CVD) outcomes (incident CVD events including all-cause mortality, CVD mortality, non-fatal CVD events, new diagnosis of CVD, peripheral vascular disease, congestive heart failure, major arrhythmias, and hypertension diagnosis) and specific CVD risk factors (blood pressure, key plasma lipids)?
    - What is the efficacy or association of n-3 FA in preventing CVD outcomes in people
        - Without known CVD (primary prevention)
        - At high risk for CVD (primary prevention)
        - With known CVD (secondary prevention)?
    - What is the relative efficacy of different n-3 FAs on CVD outcomes and risk factors?
    - Can the CVD outcomes be ordered by strength of intervention effect of n-3 FAs?
2. n-3 FA variables and modifiers:
    - How does the efficacy or association of n-3 FA in preventing CVD outcomes and with CVD risk factors differ in

subpopulations, including men, premenopausal women, postmenopausal women, and different age or race/ethnicity groups?

- What are the effects of potential confounders or interacting factors—such as plasma lipids, body mass index, blood pressure, diabetes, kidney disease, other nutrients or supplements, and drugs (e.g., statins, aspirin, diabetes drugs, hormone replacement therapy)?
- What is the efficacy or association of different ratios of n-3 FA components in dietary supplements or biomarkers, on CVD outcomes and risk factors?
- How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by ratios of different n-3 FAs—DHA, EPA, and ALA, or other n-3 FAs?
- How does the efficacy or association of n-3 FA on CVD outcomes and risk factors differ by source (e.g., fish and seafood, common plant oils (e.g., soybean, canola), fish oil supplements, fungal-algal supplements, flaxseed oil supplements)?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on CVD outcomes and risk factors?
- Is there a threshold or dose-response relationship between n-3 FA exposures and CVD outcomes and risk factors? Does the study type affect these relationships?
- How does the duration of intervention or exposure influence the effect of n-3 FA on CVD outcomes and risk factors?

- What is the effect of baseline n-3 FA status (intake or biomarkers) on the efficacy of n-3 FA intake or supplementation on CVD outcomes and risk factors?

3. Adverse events:
   - What adverse effects are related to n-3 FA intake or biomarker concentrations (in studies of CVD outcomes and risk factors)?
   - What adverse events are reported specifically among people with CVD or diabetes (in studies of CVD outcomes and risk factors)?

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

Populations

- Healthy adults (≥18 yr) without CVD or with low to intermediate risk for CVD
- Adults at high risk for CVD (e.g., with diabetes, cardiometabolic syndrome, hypertension, dyslipidemia, non-dialysis chronic kidney disease)
- Adults with clinical CVD (e.g., history of myocardial infarction, angina, transient ischemic attacks)
- Exclude populations chosen for having a non-CVD or non-diabetes-related disease (e.g., cancer, gastrointestinal disease, rheumatic disease, dialysis)

Interventions/Exposures

- n-3 FA supplements
- n-3 FA supplemented foods (e.g., eggs)

- n-3 FA content in diet (e.g., from food frequency questionnaires)
- Biomarkers of n-3 FA intake
- n-3 content of food or supplements must be quantified (e.g., exclude fish diet studies where only servings/week defined, Mediterranean diet studies without n-3 quantified). n-3 quantification can be of total n-3 FA, of a specific n-3 FA (e.g., ALA) or of combined EPA+DHA ("marine oil").
- Exclude n-3 FA dose ≥6 g/day (except for adverse events)
- Exclude weight loss interventions

Comparators

- Placebo or no n-3 FA intervention
- Different n-3 FA source intervention
- Different n-3 FA concentration intervention
- Different n-3 FA dietary exposure (e.g., comparison of quantiles)
- Different n-3 FA biomarker levels (e.g., comparison of quantiles)

Outcomes

- All-cause mortality
- Cardiovascular, cerebrovascular, and peripheral vascular events:
    - Fatal vascular events (e.g., due to myocardial infarction, stroke)
    - Non-fatal vascular events (e.g., myocardial infarction, stroke/cardiovascular accident, transient ischemic attack, unstable angina)
    - Coronary heart disease, new diagnosis
    - Congestive heart failure, new diagnosis
    - Cerebrovascular disease, new diagnosis
    - Peripheral vascular disease, new diagnosis

    - Ventricular arrhythmia, new diagnosis
    - Supraventricular arrhythmia, new diagnosis
    - Major vascular interventions/procedures (e.g, revascularization, thrombolysis, lower extremity amputation, defibrillator placement)
- Major CVD risk factors (intermediate outcomes):
    - Blood pressure (new-onset hypertension, systolic, diastolic, and mean arterial pressure)
    - Key plasma lipids (i.e., high density lipoprotein cholesterol [HDL-c], low density lipoprotein cholesterol [LDL-c], total/HDL-c ratio, LDL-c/HDL-c ratio, triglycerides)
- Adverse events (e.g., bleeding, major gastrointestinal disturbance), only from intervention studies of supplements

Timing

- Clinical outcomes, including new-onset hypertension (all study designs): ≥1 year followup (and intervention duration, as applicable)
- Intermediate outcomes (blood pressure and plasma lipids) (all study designs): ≥1 month followup
- Adverse events (all study designs): no minimum followup

Setting

Community-dwelling (non-institutionalized) individuals

Study Design

- Randomized Controlled Trials (RCTs) (all outcomes)
- Randomized cross-over studies (blood pressure and plasma lipids, adverse events), minimum washout period to be determined

- Prospective nonrandomized comparative studies (clinical outcomes, adverse events)
- Prospective cohort (single group) studies, where groups are compared based on n-3 FA intake or intake biomarker values (clinical outcomes)
- Exclude: Retrospective or case control studies or cross-sectional studies (but include prospective nested case control studies). Studies must have measure of intake prior to outcome.
- Minimum sample sizes (All outcomes: To be determined)
- English language publications

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