Evidence-based Practice Center Systematic Review Protocol

Project Title: Vitamin D and Calcium: A Systematic Review of Health Outcomes

I. Background and Objectives for the Systematic Review

The Institute of Medicine (IOM) establishes Dietary Reference Intakes (DRIs), nutrient reference values based on current knowledge about the roles of the various nutrients in human health. The DRIs—which comprise estimated average requirements (EARs), adequate intakes (AIs; set in the absence of sufficient evidence to set an EAR), and upper limits (ULs; the highest level of intake likely to pose no health risk to most individuals)—form the basis of dietary guidance for the United States and Canada. The first DRI report, released in 1997, based the recommended levels of vitamin D and calcium on the role of these nutrients in bone health.[1]

In 2009, based in part on increasing interest in the potential roles of calcium and vitamin D in preventing chronic disease (beyond their roles in preventing acute deficiency states) and physicians' increasing use of laboratory tests to assess vitamin D and calcium status among patients, the U.S. and Canadian governments requested that the IOM review the literature assessing the potential role of these nutrients in human health outcomes. The Committee to Review Dietary Reference Intakes for Vitamin D and calcium commissioned the Agency for Healthcare Research and Quality (AHRQ) to conduct a systematic review, the results of which would form part of the basis for the update to the 1997 DRIs report.[2] The IOM report noted the lack of strong evidence for an association of vitamin D and calcium status with conditions other than bone health and the need to continue relying on the latter as a basis for making recommendations—reflecting, in part, the challenges associated with assessing the role of nutrients in the etiology of chronic diseases and using such outcomes in setting recommendations for optimal intakes.[3]

Research aimed at identifying vitamin D and calcium intakes associated with increased or decreased health risks present several unique challenges. Unlike that of other nutrients, vitamin D status reflects not only dietary intake but also synthesis in response to sun exposure. Further, assessing vitamin D intake is hampered by changing or insufficient information on fortification and food levels.[4] Thus, at present, assessment of serum vitamin D levels appears to provide the closest reflection of physiological status. However, the results of the various serum assays are not strictly comparable with each other or with historical values.[5,6] Evidence suggests current laboratory reference ranges may be too high,[7] which would result in too many individuals being wrongly diagnosed as having vitamin D deficiency. Further, health outcomes that depend on vitamin D may not strictly reflect vitamin D status, in part because of the strong interdependence between vitamin D and calcium and because many vitamin D trials also administer calcium.

In preparation for a project the Office of Dietary Supplements (ODS) at the National Institutes of Health is undertaking on best clinical practices related to vitamin D in primary care settings, based on the updated DRI report, the ODS and AHRQ requested an update to the 2009 systematic review that will incorporate the findings of studies on vitamin D and vitamin D

administered in conjunction with calcium that have been conducted since the release of that review. The update report will assess all outcomes assessed in the original 2009 report with the exception of weight and growth. The update report will also stratify the findings of the previous review, as well as any newly included studies on efficacy and adverse events according to vitamin D serum assay methodology, to permit a comparison by assay method.

II. The Key Questions

Introduction

The Key Questions (KQs) that will drive the update review are identical to those that drove the original 2009 review, with several minor exceptions mandated by the sponsors. These exceptions were described above and are indicated below in the text of the KQs themselves. The PICOTS (**p**opulation, **i**ntervention, **c**omparator, outcomes, **t**iming and **s**etting) are also given for each KQ.

Key Question 1

What is the effect of vitamin D intake or combined vitamin D plus calcium intake (but not calcium intake alone) on clinical outcomes, including cardiovascular diseases, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification (the current report excludes two outcomes included in the original 2009 report:growth and weight management).

- **Population(s)**
  - The primary population of interest is generally healthy people with no known disorders, with the following exceptions. Studies that include broad populations might include some individuals with diseases or who are at risk for diseases.
  - Studies of individuals with previous cancer, previous fractures, or precancerous conditions will be included.
  - With the exception of studies of older adults, studies in which more than 20 percent of the participants have been diagnosed with a disease will be excluded.
  - For clinical outcomes of cardiovascular disease (CVD), only studies of adults will be included (≥18 years of age)

- **Interventions**
  - For observational studies (exposures):
    - Serum concentration of 25-hydroxyvitamin D [25(OH)D] or 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] and method used
    - Dietary intake of calcium from food and supplements
    - Calcium balance
  - For interventional studies:

- Vitamin D supplements with known doses
- Calcium supplements if coadministered with vitamin D
- Food-based interventions in which the doses of vitamin D and calcium were quantified and in which the doses differ between comparison groups

- **Comparators**

  - For observational studies:
    - Lower serum concentrations of vitamin D

  - For interventional studies:
    - Placebo, nonfortified/supplemented food

- **Outcomes**

  - CVD clinical outcomes
    - Cardiac events or symptoms
    - Cerebrovascular events
    - Peripheral vascular events or symptoms
    - Cardiovascular death
    - Study-specific combinations of cardiovascular events

  - Cancer (incident or mortality)
    - Total cancer
    - Prostate cancer
    - Colorectal cancer
    - Breast cancer
    - Pancreatic cancer
    - Cancer-specific mortality

  - Immune function clinical outcomes
    - Infectious disease
    - Autoimmune diseases
    - Infectious disease-specific mortality

  - Pregnancy-related outcomes
    - Preterm birth or low birth weight
    - Infant mortality

  - Mortality, all cause

  - Bone health, clinical outcomes
    - Rickets
    - Fracture
    - Falls or muscle strength

- Adverse effects of intervention(s)
  - All-cause mortality
  - Cancer and cancer-specific mortality
  - Renal outcomes
  - Soft tissue calcification
  - (Other) adverse events from vitamin D or vitamin D plus calcium supplements

- **Timing**

  - Timing of interventions or exposures will not be prespecified, with the exception that cross-sectional and retrospective case-control studies will not be included (nested case controls within prospective cohort studies will be included).
  - For studies with multiple followup periods, the longest followup times will be preferentially considered.

- **Settings**

  - Settings will not be prespecified.

Key Question 2

What is the effect of vitamin D or combined vitamin D and calcium intake on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density?

- **Populations**

  - As described for KQ 1, with the exception that for blood pressure and other CVD intermediate outcomes, only studies of adults ≥ 18 years of age will be included.

- **Interventions**
  - As described for KQ 1, with the following exceptions:
    - For CVD outcomes, only randomized controlled trials (RCTs) will be included.
    - For bone health outcomes, only RCTs of greater than 1 year in duration will be included.

- **Comparators**
  - As described for KQ 1.

- **Outcomes**
- As specified in the original 2009 report, unless otherwise noted:
  - CVD intermediate outcomes
  - Cancer intermediate outcomes (colorectal adenoma, aberrant crypt cells, and mammographic breast density)
  - Bone health intermediate outcomes (only bone mineral density/content)

    - Pregnancy-related intermediate outcomes
        - Pre-eclampsia
        - High blood pressure with or without proteinuria

- **Timing**
    - As described for KQ 1, except for intermediate bone health for which studies of less than 1 year in duration will be excluded.

- **Settings**
    - As described for KQ 1.

Key Question 3

What is the association between serum 25(OH)D concentrations and clinical outcomes?*

- **Populations**
    - As described for KQ 1.

- **Interventions**
    - Serum concentration of 25(OH)D or 1,25 $(OH)_2D$ and the method used.

- **Comparators**
    - The serum concentration of 25(OH)D or 1,25 $(OH)_2D$ and the method used for the placebo or other comparison group

- **Outcomes**
    - As described for KQ 1.

- **Timing**
    - As described for KQ 1.

- **Settings**
    - As described for KQ 1.

*The original question included the effect of calcium balance.

Key Question 4

What is the effect of vitamin D or combined vitamin D and calcium intake on serum 25(OH)D concentrations?

- **Populations** are the same as for KQ 1.

- **Interventions**
    - Randomized controlled trials (RCTs) identified to answer all other KQs.

- **Comparators**
  - Placebo or lower dose supplement

- **Outcomes**
  - Dose-response relationship between intake levels and indices of exposure

- **Timing**
  - As described for KQs 1 and 2

- **Settings**
  - As described for KQs 1 and 2

Key Question 5

What is the association between serum 25(OH)D concentration and surrogate or intermediate outcomes?

- **Populations**
  - As described for KQ 2

- **Interventions**
  - As described for KQ 2

- **Comparators**
  - As described for KQ 2

- **Outcomes**
  - As described for KQ 2

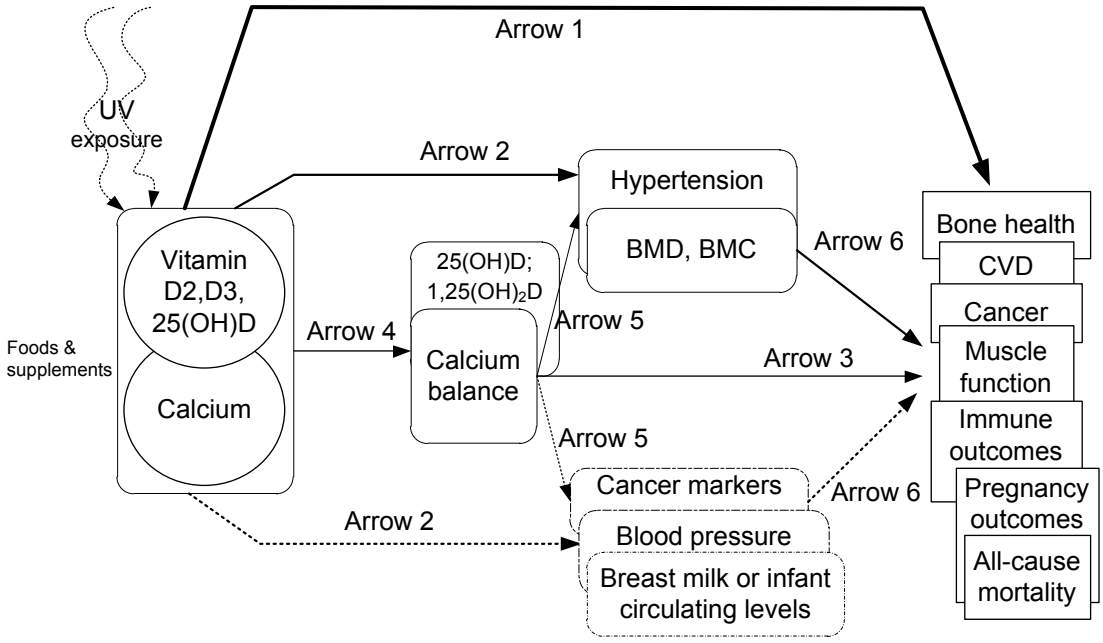
- **Timing**
  - As described for KQ 2

- **Settings**
  - As described for KQ 2

III. Analytic Framework

Two analytic frameworks are provided from the original 2009 report (labeled as Figure 1 and Figure 2 below). Alternate text legends (for Section 508 compliance) for both figures are included in Appendix A.

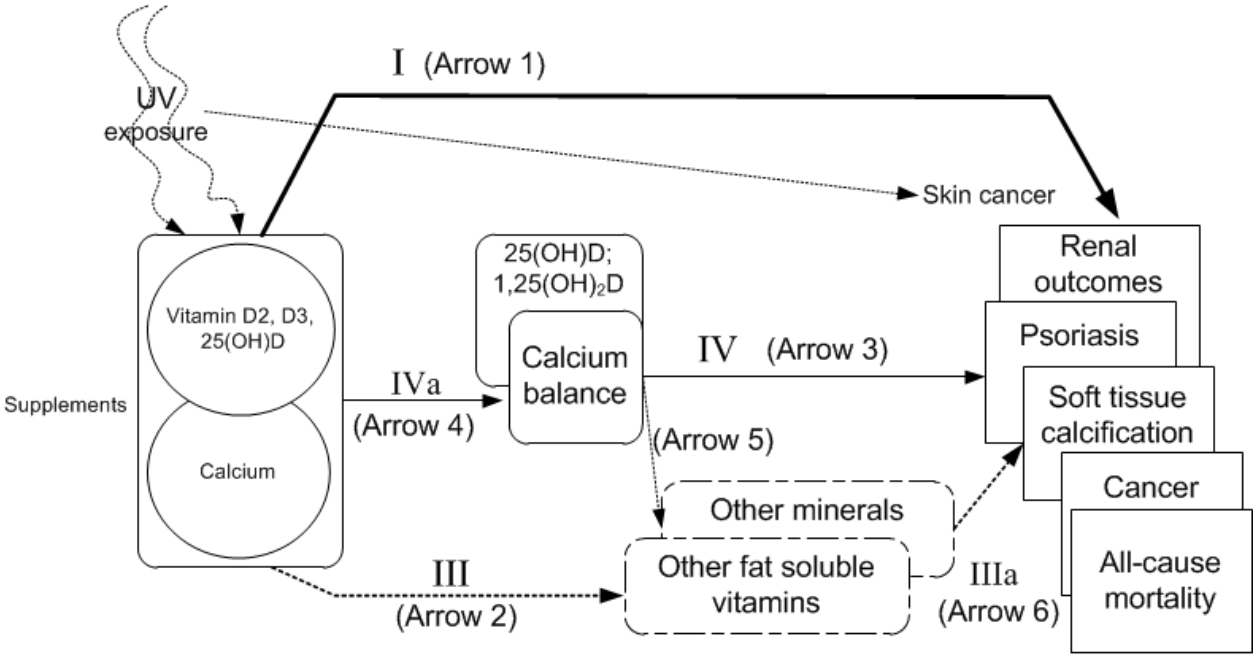
Figure 1. Analytic framework for vitamin D and/or calcium Estimated Average Requirements (EARs)



Arrow 1 indicates the association of exposure with clinical outcomes of interest.
Arrow 2 indicates the association of exposure with surrogate or intermediate outcomes that have, respectively, good or possible evidence for linkage with clinical outcomes. Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with a dashed outline.
Arrow 3 indicates the association of indicators of exposure to clinical outcomes.
Arrow 4 indicates the association between exposure and indicators of exposure.
Arrow 5 indicates the association of indicators of exposure to surrogate or intermediate outcomes.
Arrow 6 indicates the association between surrogate or intermediate outcomes and clinical outcomes.

Abbreviations: $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D;BMC = bone mineral content; BMD = bone mineral density; CVD = cardiovascular disease; UV = ultraviolet light

Figure 2. Analytic framework for vitamin D and/or calcium Upper Limits



Arrow 1 indicates the association of exposure with clinical outcomes of interest.
Arrow 3 indicates the association of indicators of exposure to clinical outcomes.
Arrow 4 indicates the association between exposure and indicators of exposure

Abbreviations: 1,25(OH)2D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; UV = ultraviolet light

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The eligibility criteria for article inclusion will be identical to those used in the original 2009 report, with the exceptions noted. The original report noted that because of the wide range of outcomes for which data needed to be sought, it was not possible to apply the same eligibility criteria across all categories of outcomes. Only studies of humans, published in the English language, will be included.

Populations of Interest

The primary population of interest is generally healthy people with no known disorders. Studies that include a broad population that might include some people with diseases of concern—for example, some hypertensive and diabetic patients—will be included. People with previous cancer (or cancer survivors), previous fractures, and precancerous conditions (e.g., colon polyps) will be included. Studies that enroll more than 20 percent of subjects with any diseases at baseline will be excluded, with the following exceptions. An exception will be made

for older adults (mean age ≥ 65 years) due to a high prevalence of diseases in this population. For studies of older adults, studies that exclusively enroll subjects with particular diseases (e.g., 100% with type 2 diabetes) will be excluded. In addition, for studies of blood pressure, studies of people exclusively with hypertension will be included. For studies of cancer recurrence, populations that comprise only those with previous cancer will be included. For upper limit (adverse event [AE]) outcomes, we will include any adverse effects of high intake in any population.

Age limitations will be as specified for each KQ and outcomes as outlined above. Study size will not be considered an exclusion criterion.

Intervention/Exposure of Interest

We will include interventional studies (controlled trials) of vitamin D supplements (but not analogues) of known doses, vitamin D plus calcium supplements of known doses (any other combination of supplements will be excluded, unless the independent effects of vitamin D can be separated; studies of multivitamins are excluded); and food-based interventions if the doses of vitamin D or vitamin D plus calcium are quantified and differ from the comparison group. Studies of nonoral routes of nutrient delivery will be excluded.

We will include observational studies that report exposures as the serum concentrations of 25(OH)D or $1,25(OH)_2D$ and calcium, dietary intake level of calcium from food and/or supplements, or calcium balance. Observational studies reporting exposures as the dietary intake level of vitamin D will not be included due to the inadequacy of nutrient composition tables for vitamin D.

Specific Outcomes of Interest

These comprise the following clinical and related intermediary outcomes:

- CVD clinical outcomes (cardiac events or symptoms [e.g., myocardial infarction, angina]; cerebrovascular events [stroke; transient ischemic attacks]; peripheral vascular events or symptoms [diagnosis; claudication]); cardiovascular death; and study-specific combinations of cardiovascular events
- CVD intermediate outcomes (diagnosis of hypertension, blood pressure, incident overweight or obesity, body mass index, or weight [it will be necessary to clarify whether body mass index and weight outcomes are to be retained if assessed as CVD intermediary outcomes])
- Cancer (incidence or mortality) clinical outcomes, including prostate, colorectal cancer, breast cancer, pancreatic cancer, and cancer-specific mortality.
- Cancer intermediate outcomes, including colorectal adenoma aberrant crypt foci and mammographic breast density (quantitative whole-breast density)
- Immune function clinical outcomes (infectious diseases, autoimmune diseases, infectious disease-specific mortality)
- Pregnancy-related clinical and intermediate outcomes (preterm birth, infant mortality or low birth weight, high blood pressure with or without proteinuria, pre-eclampsia)
- All-cause mortality

- Bone health clinical outcomes (rickets, fracture, falls, or muscle strength)
- Bone health intermediate outcomes (bone mineral density or content)
- Dose-response relationship between intake levels and indicators of exposure (serum concentration of 25(OH)D, breast milk, or circulating concentrations of 25(OH)D in infants)
- Outcomes of tolerable upper intake levels (ULs/AEs; specifically, all-cause mortality; cancer and cancer-specific mortality, renal outcomes, and soft tissue calcification)

Study Design

We will include RCTs; nonrandomized, prospective comparative studies of interventions; prospective, longitudinal observational studies (where the measure of exposure occurred before that of the outcome(s)); and prospective nested case-control studies (case-control studies nested in a cohort so the measure of exposure occurs before that of the outcomes). Also included will be prior systematic reviews deemed relevant to a specific KQ and published since the original 2009 report; systematic reviews will also be reviewed for any original studies missed by the literature searches.

Excluded studies will be cross-sectional studies and traditional, retrospective case-control studies (where the measure of exposure occurred after or concurrently with the outcome).

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The search strategy of peer-reviewed literature will duplicate that used in the original 2009 report, excluding the searches specific to calcium only and those for the outcomes of growth and weight. The librarian at the RAND Southern California Evidence-based Practice Center will review and modify the search strategies as needed and run the searches in PubMed® and the Cochrane Central Database from January 2008 to the present (Appendix B). The search will be updated after the draft report is submitted.

To assess the status of ongoing and recently completed trials, we will search ClinicalTrials.gov. In addition, a notice will be placed in the *Federal Register* requesting scientific information packets and the results of unpublished studies from supplement manufacturers.

Study selection will be conducted as described in the original 2009 report[2] and in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).[8] In brief, the output of the literature searches will be entered into the DistillerSR database (Evidence Partners, Inc., Ottawa, Ontario, Canada) for screening. A list of inclusion and exclusion criteria will be developed. After practice screening of a random selection of 100 titles, titles and abstracts will be dually screened, with all selections going on for full-text review. Inclusion decisions about full-text articles will be reconciled, with disagreements settled by the project lead and the reasons for exclusion recorded. Before drafting the report, we will ask the Technical Expert Panel (TEP) to review the list of included and excluded studies against the inclusion/exclusion criteria for any omissions. We will review any studies suggested by peer or public reviewers against the inclusion/exclusion criteria.

C. Data Abstraction and Data Management

The data to be abstracted from included studies are those abstracted for the original 2009 report, as shown in the data abstraction forms for RCTs and observational studies included in Appendix C.

Data abstraction forms will be developed using the Systematic Review Data Repository™. The forms will be piloted with 10 randomly selected studies (five RCTs and five observational studies) among the reviewers and any necessary changes made. Study-level conditions will be abstracted in duplicate and reconciled by the project's administrative assistant and the reviewers. Disagreements will be settled by the project lead or co-project lead. Efficacy and safety data will be abstracted by the statistical analyst and confirmed by the co-project lead. The statistical analyst will also track multiple articles reporting on the same study to prevent collection of duplicate data. Any questions will be referred to the co-project lead, including questions regarding the assay method used to assess 25(OH)D.

The following items will be extracted: study characteristics, baseline population characteristics (age; sex; race/ethnicity; residential status for elderly [home, institution]; health conditions; comorbidities; baseline vitamin D/calcium status; baseline body mass index, if relevant; bone mineral density or bone mineral content, if relevant), background diet data, dietary assessment methods for calcium intake, 25(OH)D and $1,25(OH)_2D$ assay methods, interventions and comparators (for interventional studies only: if the type of vitamin D supplement [D2 or D3] is clearly reported, we will extract and report this information); confounders and effect modifiers that will be adjusted for in the statistical analysis; outcomes; and quality assessment items (see section D, below). Evidence tables will be constructed to display this information.

D. Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias (ROB) will be assessed using the identical criteria used in the original 2009 report to ensure continuity, as described below. ROB will be assessed at the study level in duplicate for each published study.

For RCTs, items to be assessed will include the methods used for randomization, allocation concealment, and blinding, as well as the use of intention-to-treat analysis, the report of well-described valid primary outcomes, and the dropout rate.

For interventional studies with a nonrandomized design, we will use the reported eligibility criteria and will assess the adequacy of controlling for differences between study arms with respect to baseline characteristics and prognostic factors. We will also assess the reporting of intention-to-treat analyses and crossovers when so designed, as well as important differential loss to followup between study arms or overall high loss to followup. The validity and the adequate description of outcomes and results will also be assessed.

For the assessment of prospective cohorts and nested case-control studies, we will apply a rating checklist specifically designed for nutritional epidemiology studies based on some of the reporting items for cohort studies in STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist[9] and the nutrition-specific items in a previous publication[10] by the authors of the original 2009 report. Items to be assessed include eligibility criteria and sampling of the study population, blinding of exposure and outcome assessors, dietary assessment methodology (when applicable), assay methodology for biomarkers of intake (when

applicable), clear reporting of comparisons in the study, statistical analyses, adequacy of controlling for baseline characteristics and prognostic factors (including confounders), clear reporting of outcome definitions, and a prospective study design with preplanned hypotheses.

Overall study quality will be rated on a letter scale of A to C, as done in the original 2009 report and adapted from the AHRQ *Methods Guide* in use in 2009. Several additional criteria will be considered in assigning a ROB grade. For RCTs, the additional criteria include cross-arm contamination, and for observational studies of cancer outcomes, the additional criteria include diagnostic ascertainment.

E. Data Synthesis

Data and study characteristics abstracted from new studies will be added to the evidence tables from the original 2009 report. Columns will be added to the evidence tables to indicate the serum vitamin D assay method, where not already indicated. The Request for Task Order Proposals for the evidence review stipulated that the data from any new studies be added to the tables and figures of the original report, indicating the original findings as well as the new findings. Columns will be added to the data tables showing the serum assay method for vitamin D. Subfigures will be added to the figures depicting the relationships between doses of vitamin D supplementation and net changes in the serum vitamin D concentration to show stratification by assay method.

The original report included only one meta-analysis, a revision of a meta-analysis of a previously published data set with different inclusion and exclusion criteria. It is not anticipated that new meta-analyses will be conducted, based on familiarity with the heterogeneity of the data in prior studies. Thus, in addition to summarizing the data in tables and bubble figures, we will summarize the study outcomes qualitatively for each KQ and sub-KQ of interest. Meta-regressions/sensitivity analyses and subgroup analyses are not anticipated, unless the TEP recommends otherwise. Results of any unpublished studies will be provided in an appendix and will not be considered in the report text.

F. Grading the Strength of Evidence for Individual Comparisons and Outcomes

The original 2009 report did not evaluate the overall strength of evidence (SOE), as such. If desired, we will grade the SOE, based on the AHRQ *Methods Guide* (chapter 10[11]). The most likely target outcomes for SOE assessment will be clinical outcomes of RCTs with three or more studies reporting data. The domains to be included are ROB, consistency, directness, reporting bias, and dose response. However, the study-level factors necessary to make these judgments may not be available for the studies in the original report. Therefore, the ability to assess the overall SOE across old and new studies will depend on the availability of those assessments and human resources.

G. Assessing Applicability

As for evaluation the overall SOE, applicability will be assessed for each body of evidence based on population age, health status, race/ethnicity, setting (e.g., residential status for older

adults), baseline vitamin D and calcium status, intervention or exposure doses (relative to comparators), and study durations based on the AHRQ *Methods Guide* (chapter 6[12]).

V. References

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10. Chung M, Balk EM, Ip S, et al. Reporting of systematic reviews of micronutrients and health: a critical appraisal. Am J Clin Nutr. 2009 Apr;89(4):1099-113. PMID: 19244363.
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12. Atkins D, Chang S, Gartlehner G, et al. Assessing the applicability of studies when comparing medical interventions. In: Methods Guide for Effectiveness and Comparative

Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2012:98-111. Available at http://effectivehealthcare.ahrq.gov/ehc/products/60/318/MethodsGuide_Prepublication-Draft_20120523.pdf.

VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale. Changes made to the protocol will be noted in section VII of the protocol in a tabular format (see below); the date of the amendment will be noted at the top of the protocol.

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol.	Specify where the change would be found in the protocol.	Describe the language of the original protocol.	Describe the change in the protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use a justification such as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

For all Evidence-based Practice Center (EPC) reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

Key Informants will be included at the discretion of the partner, the Office of Dietary Supplements of the National Institutes of Health.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

As specified in the amendment to the Request for Task Order Proposal, a small TEP composed of members of the TEP for the original 2009 report will be assembled. The TEP will be asked to review the Key Questions and to provide methodological assistance with the specific task of stratifying outcomes by the 25(OH)D serum assay methodology used.

Disclosures of financial or nonfinancial conflict of interest will be submitted for each prospective TEP member.

XI. Peer Reviewers

A list of prospective peer reviewers and their affiliations and qualifications will be provided to the TOO by September 13, 2013, along with disclosures of conflict of interest, as specified in the Delivery Schedule.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest which cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

Disclosures of conflict of interest were submitted for the EPC core team investigators before the project kickoff call.

XIII. Role of the Funder

This project was funded under Contract No. 290-2012-00006-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.