CRN Comments - **FINAL**

Topic:

USPSTF Draft Research Plan for Vitamin D Deficiency in Adults: Screening.

Background:

The U.S. Preventive Services Task Force (USPSTF) is an independent, volunteer panel of national experts in prevention and evidence-based medicine. The Task Force works to improve the health of all Americans by making evidence-based recommendations about clinical preventive services such as screenings, counseling services, and preventive medications. All recommendations are published on the Task Force's website and/or in a peer-reviewed journal.

On October 25, 2018, the USPSTF released a draft of its *Research Plan for Vitamin D Deficiency in Adults: Screening.* The research plan will be used to guide a systematic review of the evidence by researchers at an Evidence-based Practice Center. The resulting Evidence Review will form the basis of the updated USPSTF Recommendation Statement on screening for vitamin D deficiency in adults. In 2014, USPSTF concluded that the state of the evidence at the time was insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

Due Date: Comments are due November 21, 2018.

Draft CRN response to USPSTF Questions below:

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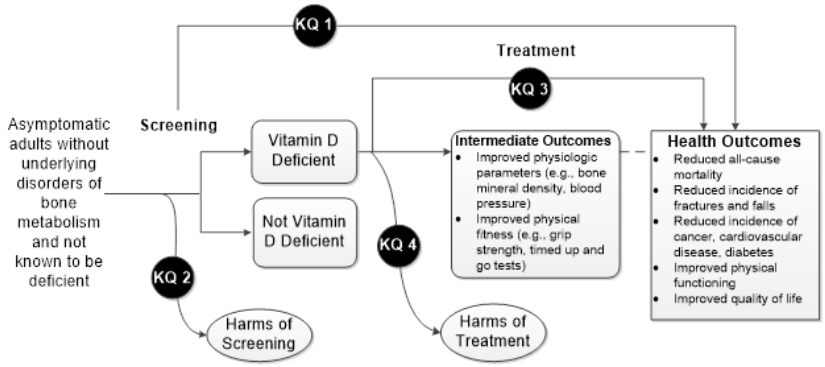
Proposed Analytic Framework



Abbreviation: KQ = Key Question.

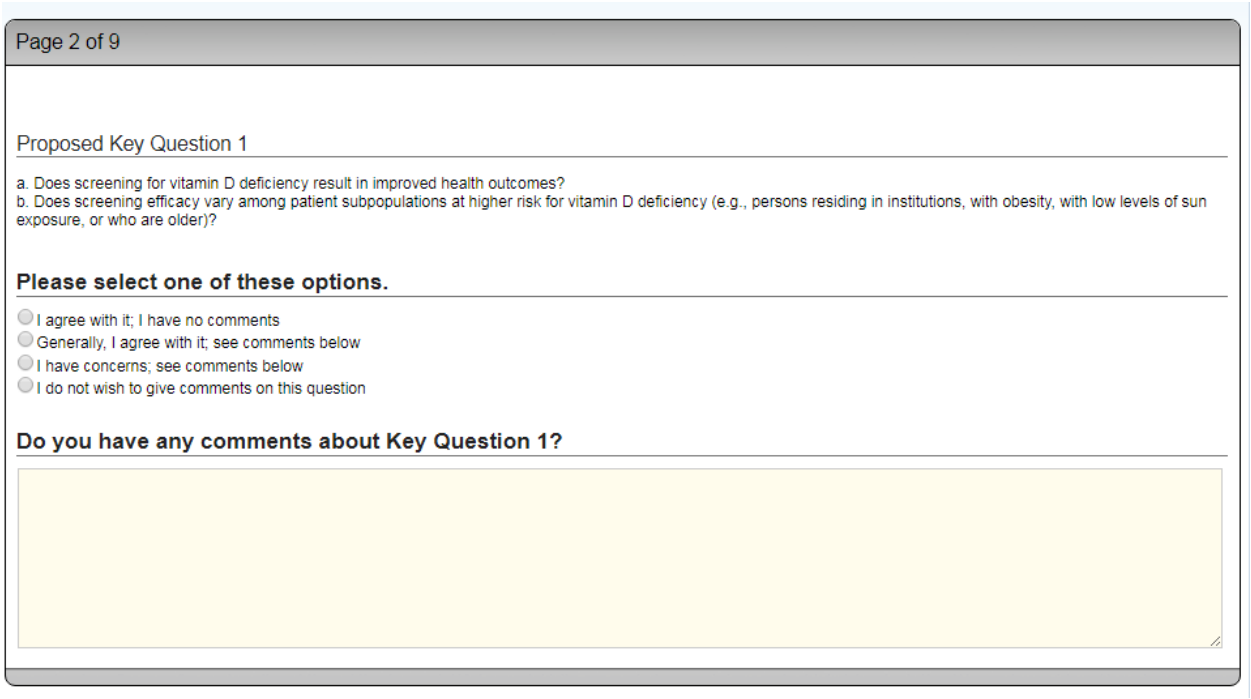
Please select one of these options.

- I agree with it; I have no comments
- Generally, I agree with it; see comments below
- I have concerns; see comments below
- I do not wish to give comments on this question

Do you have any comments about the Analytic Framework?

CRN Response: Generally, I agree with it, see comment below

CRN Comment: While evaluating the effect of a nutritional intervention on chronic disease and mortality risk is important, intermediate outcomes are also essential to inform clinicians in providing recommendations to patients. With a greater focus on proactive rather than reactive healthcare, assessing intermediate outcomes such as improved physiologic parameters and physical fitness can help healthcare providers make recommendations to patients for maintaining wellness. Further, attempting to confirm the effect of vitamin D treatment on broad, long latency endpoints such as all-cause mortality or cancer within the context of other vitamin D sources (e.g., dietary and sunlight exposure) is complicated by many confounding variables. Therefore, CRN suggests that the effect of vitamin D screening and treatment on important intermediate outcomes such as bone mineral density, blood pressure, or improved physical fitness are equally important questions that deserve a full systematic review.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Proposed Key Question 1

a. Does screening for vitamin D deficiency result in improved health outcomes?
b. Does screening efficacy vary among patient subpopulations at higher risk for vitamin D deficiency (e.g., persons residing in institutions, with obesity, with low levels of sun exposure, or who are older)?

Please select one of these options.

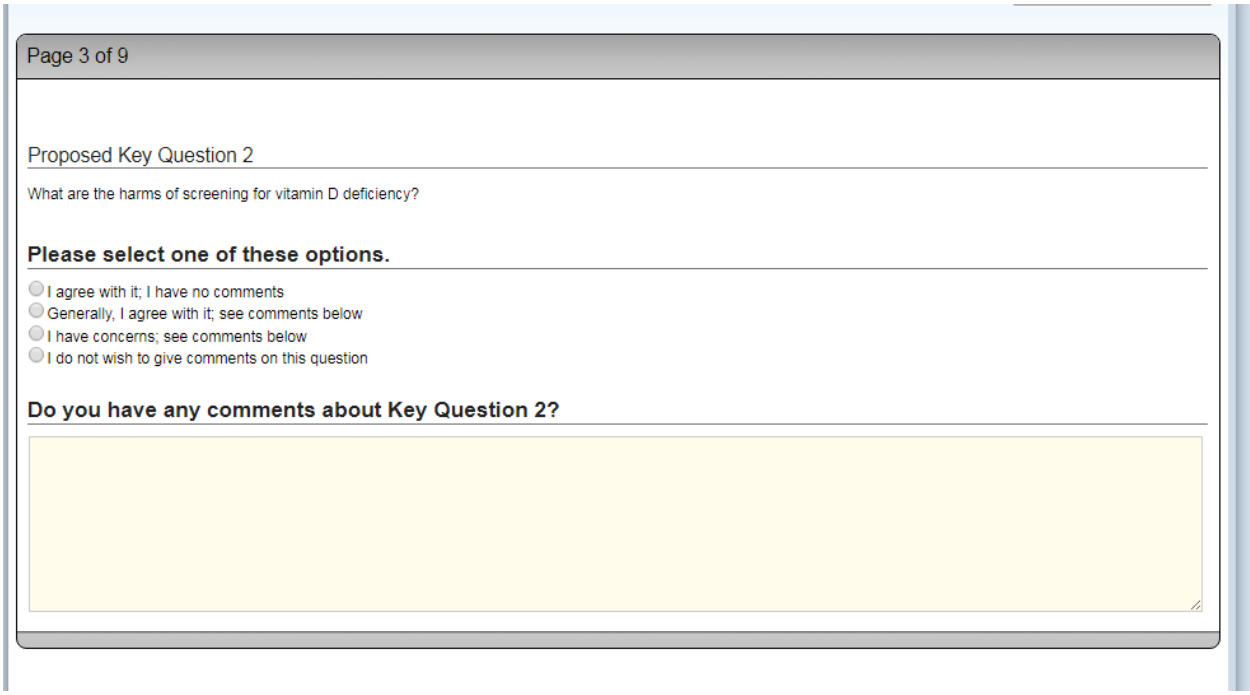
- I agree with it; I have no comments
- Generally, I agree with it; see comments below
- I have concerns; see comments below
- I do not wish to give comments on this question

Do you have any comments about Key Question 1?

CRN Response: Generally, I agree with it; see comments below.

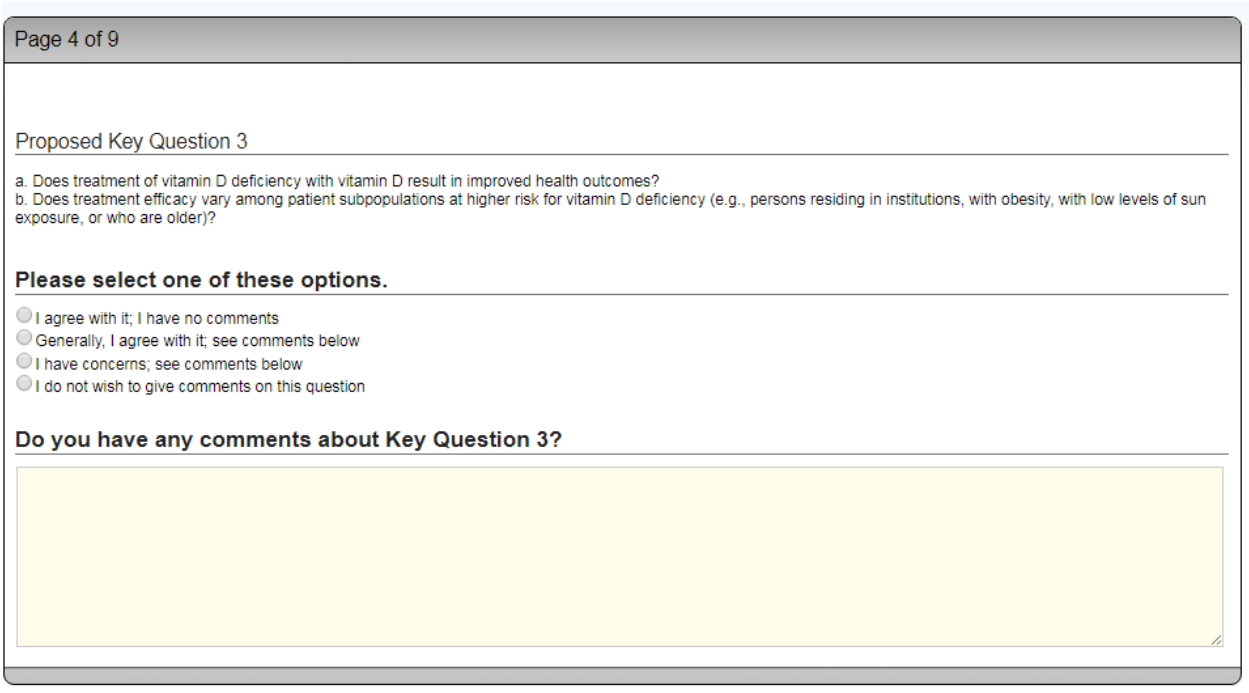
CRN Comment: CRN recommends that USPSTF add a sub-part "c" to Key Question 1 regarding the relationship between screening for vitamin deficiency and intermediate health outcomes. For example:

Key Question 1c: Does screening for vitamin D deficiency result in improved intermediate outcomes?



CRN Response: I have concerns, see comments below.

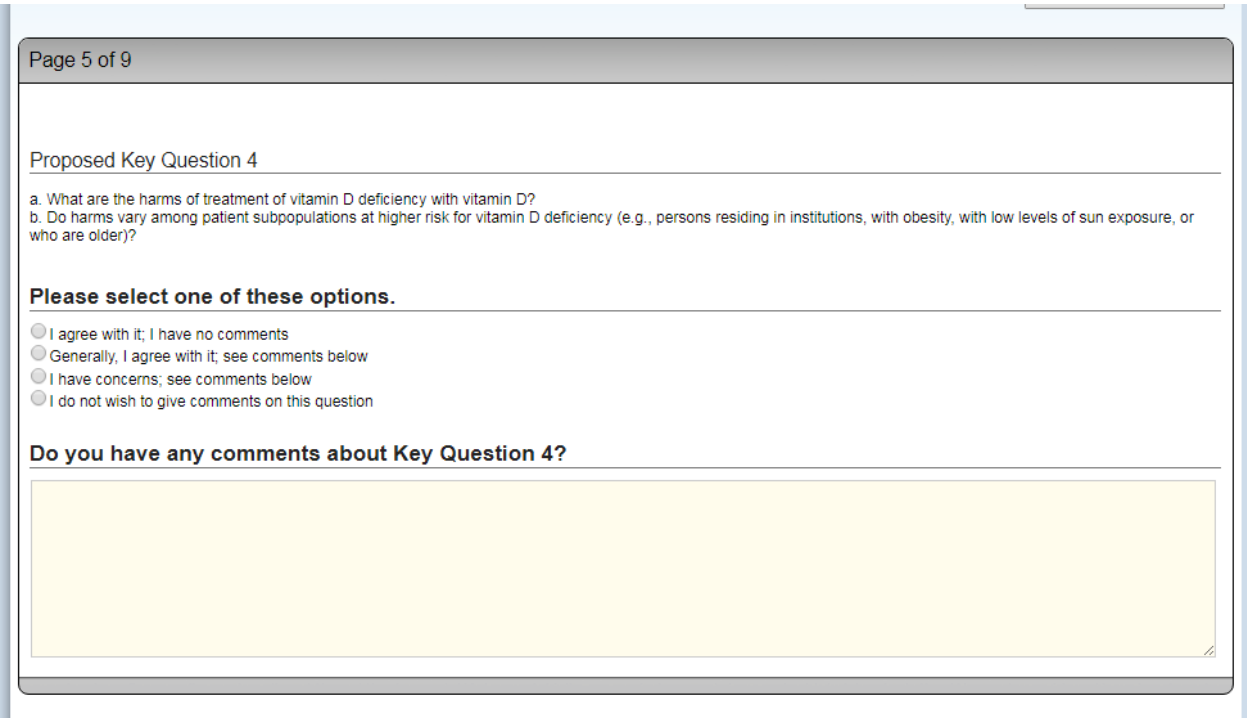
CRN Comment: Key Question #2, as currently written, assumes that there are established harms that have been linked to screening for vitamin D deficiency; however, harms have not been established. Key Question #2 should be modified to: Are there harms of screening for vitamin D deficiency?



CRN Response: Generally, I agree with it; see comments below.

CRN Comment: CRN recommends that USPSTF add a sub-part “c” for Key Question 3 regarding the relationship between treatment of vitamin D deficiency with vitamin D and intermediate outcomes. For example:

Key Question 3c: Does treatment of vitamin D deficiency with vitamin D result in improved intermediate outcomes?

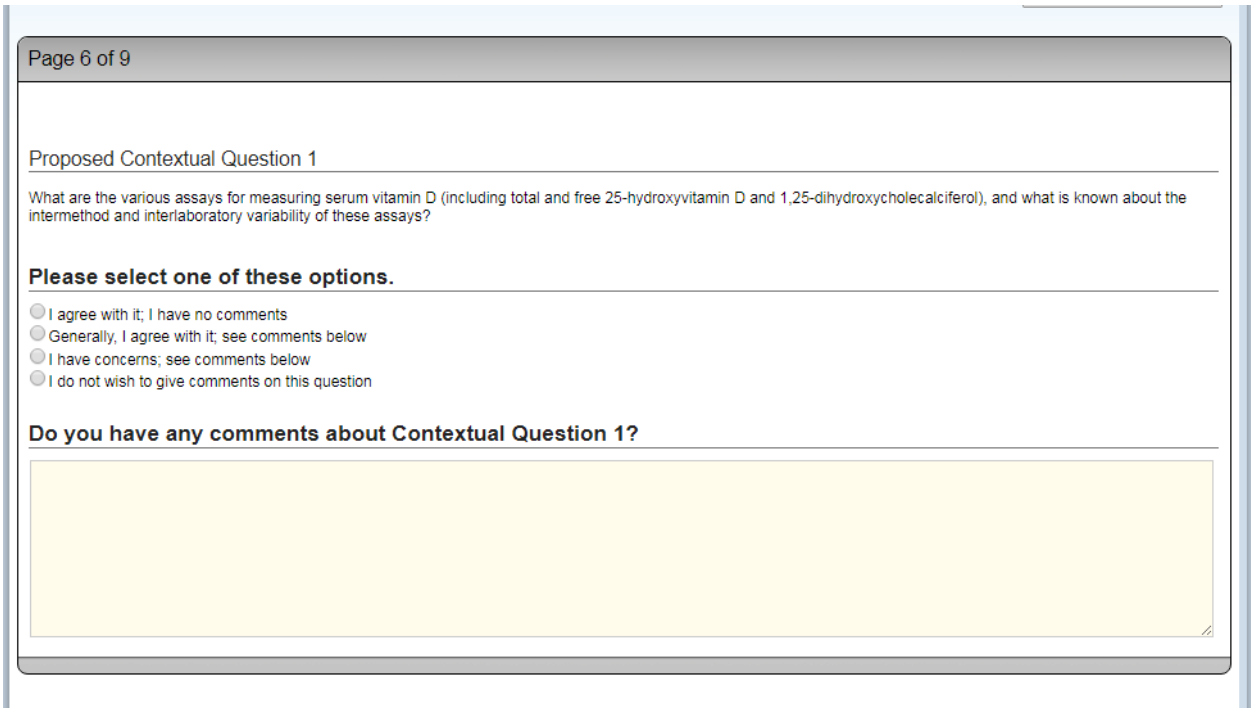


CRN Response: I have concerns, see comments below.

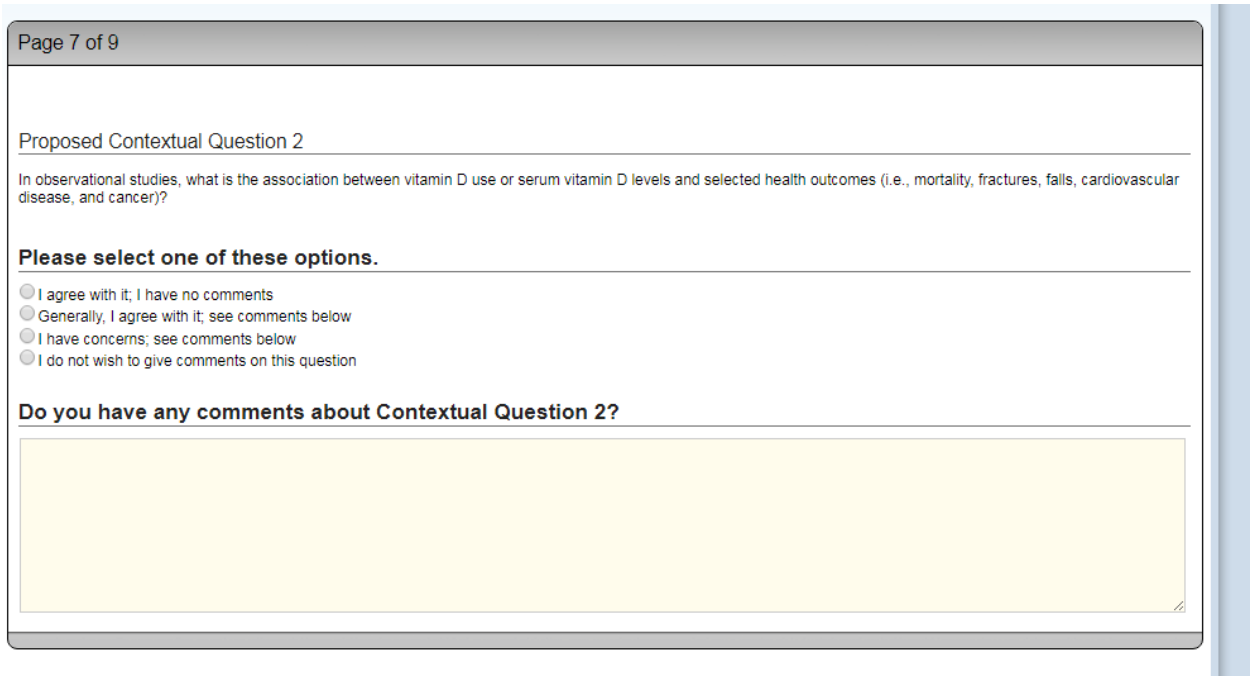
CRN Comment: Key Question 4a, as currently written, assumes that there are established harms that have been linked to treatment of vitamin D deficiency with vitamin D; however, harms have not been established.

Key Question 4a should be modified to: Are there harms of treatment of vitamin D deficiency with vitamin D?

Similarly, Key Question 4b should be modified to: For any harms identified in Key Question 4a, do these harms vary among patient subpopulations at higher risk for vitamin D deficiency (e.g., persons residing in institutions, with obesity, with low levels of sun exposure, or who are older)?



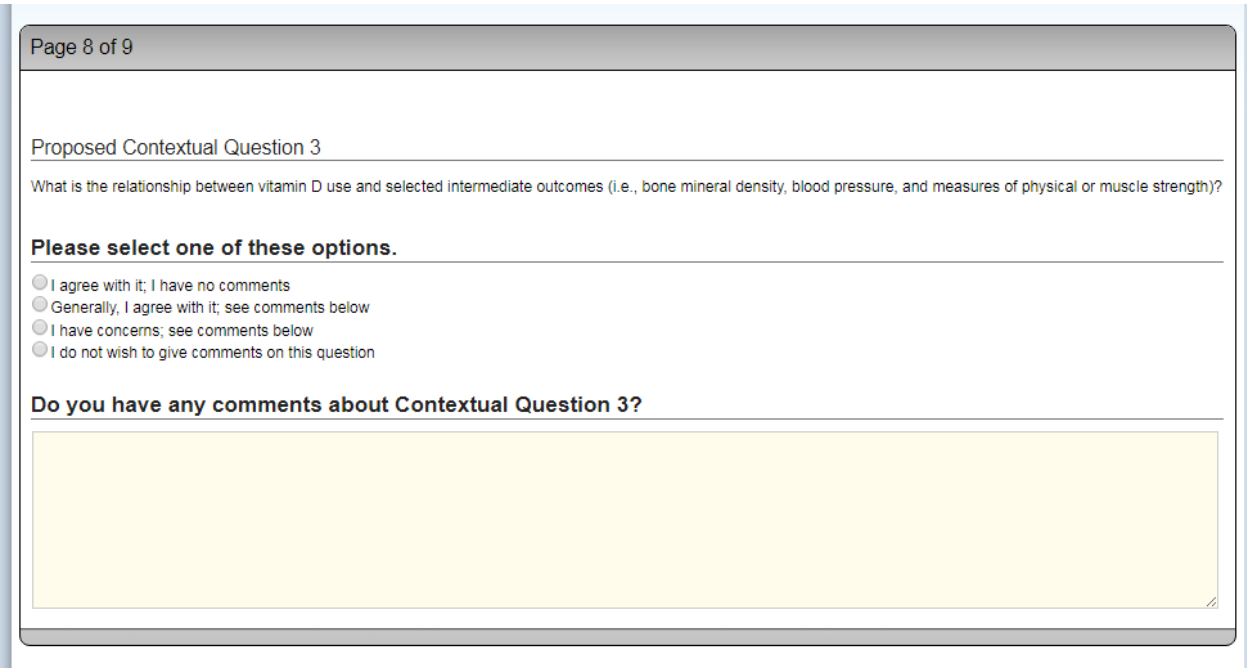
CRN Response: I do not wish to give comments on this question



CRN Response: Generally, I agree with it, see comments below

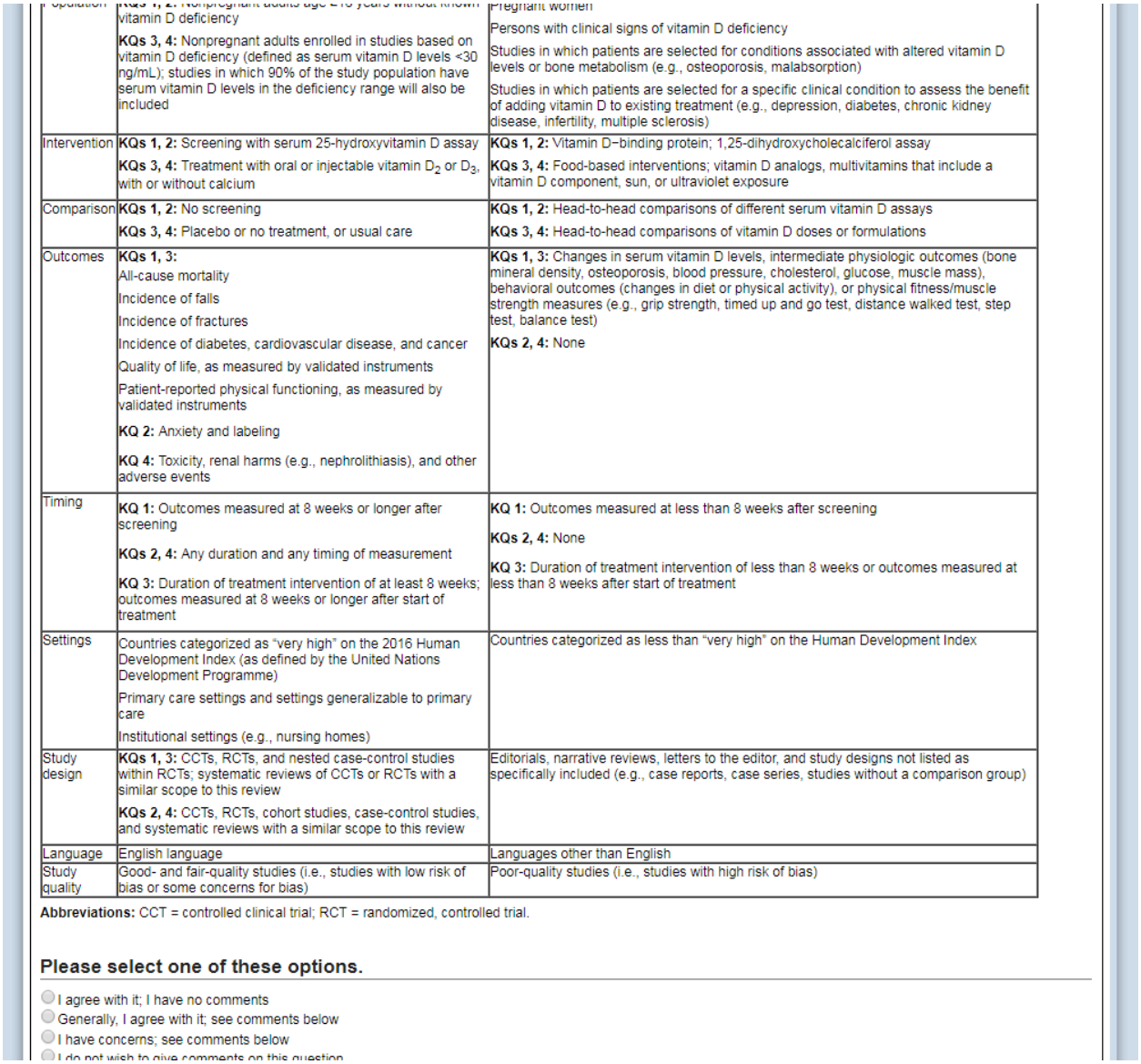
CRN Comment: It is critical to closely evaluate serum vitamin D levels and how they correlate with selected health outcomes. Studies that only assess supplemental

vitamin D do not account for individual diet or sun exposure and inter- subject variability in absorption, digestion, and metabolism of vitamin D. Serum vitamin D levels reflect individual vitamin D status and are a more informative variable to assess against selected health outcomes.



CRN Response: I have concerns, see comment below

CRN Comment: CRN recommends that in lieu of Contextual Question 3, USPSTF add new subparts to Key Question 1 and Key Question 3 regarding the relationships between screening for vitamin D deficiency and treatment of vitamin D deficiency with vitamin D, respectively, and intermediate outcomes. While evaluating the effect of a nutritional intervention on chronic disease and mortality risk is important, intermediate outcomes are also essential to inform clinicians in providing recommendations to patients. With a greater focus on proactive rather than reactive healthcare, assessing intermediate outcomes such as improved physiologic parameters and physical fitness can help healthcare providers make recommendations to patients for maintaining wellness. Further, attempting to confirm the effect of vitamin D treatment on broad, long latency endpoints such as all-cause mortality or cancer within the context of other vitamin D sources (e.g., dietary and sunlight exposure) is complicated by many confounding variables.



	vitamin D deficiency **KQs 3, 4:** Nonpregnant adults enrolled in studies based on vitamin D deficiency (defined as serum vitamin D levels <30 ng/mL); studies in which 90% of the study population have serum vitamin D levels in the deficiency range will also be included	Pregnant women Persons with clinical signs of vitamin D deficiency Studies in which patients are selected for conditions associated with altered vitamin D levels or bone metabolism (e.g., osteoporosis, malabsorption) Studies in which patients are selected for a specific clinical condition to assess the benefit of adding vitamin D to existing treatment (e.g., depression, diabetes, chronic kidney disease, infertility, multiple sclerosis)
Intervention	**KQs 1, 2:** Screening with serum 25-hydroxyvitamin D assay **KQs 3, 4:** Treatment with oral or injectable vitamin D_2 or D_3, with or without calcium	**KQs 1, 2:** Vitamin D–binding protein; 1,25-dihydroxycholecalciferol assay **KQs 3, 4:** Food-based interventions; vitamin D analogs, multivitamins that include a vitamin D component, sun, or ultraviolet exposure
Comparison	**KQs 1, 2:** No screening **KQs 3, 4:** Placebo or no treatment, or usual care	**KQs 1, 2:** Head-to-head comparisons of different serum vitamin D assays **KQs 3, 4:** Head-to-head comparisons of vitamin D doses or formulations
Outcomes	**KQs 1, 3:** All-cause mortality Incidence of falls Incidence of fractures Incidence of diabetes, cardiovascular disease, and cancer Quality of life, as measured by validated instruments Patient-reported physical functioning, as measured by validated instruments **KQ 2:** Anxiety and labeling **KQ 4:** Toxicity, renal harms (e.g., nephrolithiasis), and other adverse events	**KQs 1, 3:** Changes in serum vitamin D levels, intermediate physiologic outcomes (bone mineral density, osteoporosis, blood pressure, cholesterol, glucose, muscle mass), behavioral outcomes (changes in diet or physical activity), or physical fitness/muscle strength measures (e.g., grip strength, timed up and go test, distance walked test, step test, balance test) **KQs 2, 4:** None
Timing	**KQ 1:** Outcomes measured at 8 weeks or longer after screening **KQs 2, 4:** Any duration and any timing of measurement **KQ 3:** Duration of treatment intervention of at least 8 weeks; outcomes measured at 8 weeks or longer after start of treatment	**KQ 1:** Outcomes measured at less than 8 weeks after screening **KQs 2, 4:** None **KQ 3:** Duration of treatment intervention of less than 8 weeks or outcomes measured at less than 8 weeks after start of treatment
Settings	Countries categorized as "very high" on the 2016 Human Development Index (as defined by the United Nations Development Programme) Primary care settings and settings generalizable to primary care Institutional settings (e.g., nursing homes)	Countries categorized as less than "very high" on the Human Development Index
Study design	**KQs 1, 3:** CCTs, RCTs, and nested case-control studies within RCTs; systematic reviews of CCTs or RCTs with a similar scope to this review **KQs 2, 4:** CCTs, RCTs, cohort studies, case-control studies, and systematic reviews with a similar scope to this review	Editorials, narrative reviews, letters to the editor, and study designs not listed as specifically included (e.g., case reports, case series, studies without a comparison group)
Language	English language	Languages other than English
Study quality	Good- and fair-quality studies (i.e., studies with low risk of bias or some concerns for bias)	Poor-quality studies (i.e., studies with high risk of bias)

Abbreviations: CCT = controlled clinical trial; RCT = randomized, controlled trial.

Please select one of these options.

- I agree with it; I have no comments
- Generally, I agree with it; see comments below
- I have concerns; see comments below
- I do not wish to give comments on this question

CRN Response: Generally, I agree with it, see comments below

CRN Comment: CRN recommends that USPSTF include an evaluation of the relationships between both vitamin D screening and treatment and selected intermediate outcomes. Therefore, the criteria should include, for Key Questions 1 and 3, intermediate outcomes (changes in serum vitamin D levels, intermediate physiologic outcomes (bone mineral density, osteoporosis, blood pressure, cholesterol, glucose, muscle mass), behavioral outcomes (changes in diet or physical activity), or physical fitness/muscle strength measures (e.g., grip strength, timed up and go test, distance walked test, step test, balance test). That is, KQs 1 and 3 should no longer have exclusion criteria.