Evidence-based Practice Center Systematic Review Protocol

Project Title: *The Effect of Dietary Digestible Carbohydrate Intake on Risk of Cardiovascular Disease*

I. Background and Objectives for the Systematic Review

Despite fluctuating trends in mortality rates in the last few decades,[1-3] cardiovascular disease remains the leading cause of death in the United States,[4] with a projected future increase in cardiovascular disease risk factors which include type II diabetes, hypertension, dyslipidemia, and obesity.[5] Personal and cultural dietary habits have been identified as potential risk factors associated with cardiovascular disease, particularly carbohydrate intake.[6]

Healthcare authorities and international health organizations have published guidelines for nutrients recommendations including recommendations for optimal consumed energy percentage or quantity in a form of carbohydrates intake.[7-13] Despite some inconsistencies in the methodologies and contexts, the recommendations are generally similar and recommend carbohydrates intake to be between 45% and 65% of total energy consumption, except for the WHO guidelines that recommend up to 75% of the energy to be from carbohydrates.[14] The Dietary Reference Intakes (DRI) for carbohydrates were published in 2005 and were essentially determined based on the estimated brain's requirement of glucose in different age groups taking into consideration increased physiological requirements during times of growth, pregnancy, and breast feeding. Furthermore, the adequate intake (AI) of carbohydrates for infants (age 0-12 months) was determined based on the average intake consumed in human milk and supplementary foods.[15] AI for infants under 6 months of age is 60 g/d of carbohydrates, which increases to 95 g/d between 6 and 12 months. For older children and adults of all age groups and sexes, the Required Daily Allowance (RDA) of carbohydrates is set as 130 g/d. The RDA changes to 175 g/d during pregnancy and 210 g/d during breast feeding.

Questions regarding the association between digestible carbohydrate intake and risk of cardiovascular disease have been debated with conflicting results due to the presence of numerous confounding factors that may be contributing to the risk of cardiovascular disease. Furthermore, the presence of multiple types of carbohydrates, with different glycemic indices and quality, makes establishing the effect of carbohydrate intake on cardiovascular disease even more challenging. Despite all these challenges, there has been a significant growth in the body of evidence regarding the effect of carbohydrates on cardiovascular disease (e.g., all cardiovascular events, risk of stroke, and risk of coronary heart disease) since the publication of the recommended RDI in the USA and Canada.[16-18] Evidence now links carbohydrate-rich diets to a higher risk of stroke and overall cardiovascular events.[17, 19] On the other hand, an association between high carbohydrate diet and coronary heart disease is not clearly found.[17, 19, 20]

In addition, a high carbohydrate diet has been shown in multiple observational studies to be associated with higher triglycerides levels and lower high-density lipoprotein (HDL) Cholesterol.[21-24] Interestingly, some of these studies showed a decrease in low density lipoprotein (LDL) cholesterol and total cholesterol levels in high carbohydrate diets,[21-23] but with an increase in the total cholesterol to HDL ratio.[22]

To date, the effect of digestible carbohydrates intake on blood pressure as a strong risk factor for cardiovascular disease has not been clearly determined.[25, 26] However, some data support a positive effect of low carbohydrate diet on blood pressure.[27, 28]

It should be kept in mind that the quality of carbohydrate consumed (measured by glycemic index, glycemic load, dietary carbohydrate index, carbohydrate-fiber ratio, etc.) may play a major role in altering the risks associated with carbohydrate intake.[29, 30] For example, while some systematic reviews failed to establish an association between total carbohydrate consumption and coronary heart disease, some experts argue that the carbohydrate quality that may alter the risk of coronary heart disease[31] and should be considered as a potential effect modifier.

Purpose of the Review

This systematic review and meta-analysis will evaluate the Key Question (KQ) listed below. This review intends to summarize and appraise all relevant evidence to inform the upcoming U.S. and Canadian government DRI guideline about carbohydrate intake.

II. The Key Questions (KQ)

KQ 1: What is the association between dietary digestible carbohydrate intake and the incidence of cardiovascular disease?

Please see Table 1 for inclusion and exclusion criteria by PICOTS

III. Methods

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

We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Table 1. Inclusion and Exclusion Criteria by Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Population	• Participants who are generally healthy, including participants who are determined to be overweight/obese, women who are pregnant or lactating
	• Age of participants
	  ○ Between 2 years and 9 years (before puberty)
	  ○ Between 9 and17 years
	  ○ 18 years and older
		• Participants with diseases/health-related conditions that impact carbohydrate absorption or metabolism, cancer, and malabsorption syndromes
		• Participants hospitalized with an illness or injury
		• Participants with the endpoint outcomes of CVD (i.e., studies that aim to treat participants already been diagnosed with the endpoint outcomes of interest)
		• Participants who intend to reduce weight or receive treatments for being overweight and having obesity through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions
		• Participants who are determined to be undernourished, underweight, stunted, or wasted
		• Participants who are pre-bariatric or post-bariatric surgery
		• People younger than 2 years old

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Interventions	• Total dietary digestible carbohydrate intake from foods, beverages, and dietary supplements ○ Total dietary digestible carbohydrate intake defined as collective starch and sugar intake; carbohydrate intake not including dietary fiber • A dietary pattern that quantifies the intake of total dietary digestible carbohydrates and allows the isolation of the effect of carbohydrate intake from the effect of the intake of other macronutrients	• Studies that do not specify the amount of total digestible carbohydrate intake (e.g., studies that only report type or source of digestible carbohydrate) • Studies that do not describe the entire macronutrient distribution of the diet (i.e., studies that do not report total digestible carbohydrate, total fat, and total protein contents of experimental or baseline diets) • Studies that only assess digestible carbohydrate intake via infusions (rather than the GI tract) • Studies that primarily measure postprandial responses, as opposed to longer term studies • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of digestible carbohydrate
Comparators	• Different total dietary digestible carbohydrate intake level(s)	• Comparison of different sources of carbohydrate without specifying amount of carbohydrate intake • Studies that do not attempt to control for energy intake of participants such that comparisons are made on an isocaloric basis. • Comparisons of available carbohydrate exposure should not be confounded by differences in participants' energy intake.

Outcomes	• Intermediate outcomes:
	  ○ LDL cholesterol (LDL)
	  ○ Total cholesterol (TC)
	  ○ HDL cholesterol (HDL)
	  ○ Non-HDL cholesterol
	  ○ TC:HDL ratio
	  ○ LDL:HDL ratio
	  ○ Triglycerides
	  ○ Blood pressure (systolic and/or diastolic) and hypertension
	• Final outcomes:
	  ○ Cardiovascular disease (e.g., myocardial infarction, coronary heart disease, congestive heart failure, peripheral artery disease)
	  ○ Stroke
	  ○ Cardiovascular disease-related mortality
		• Hypertensive disorders during pregnancy and/or lactation (e.g., chronic hypertension, gestational hypertension, preeclampsia-eclampsia, chronic hypertension with superimposed preeclampsia)

Timing	• At least 4 weeks	• Less than 4 weeks
Settings	• All except hospital and acute care	• Hospital and acute care

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Nonrandomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Nested case-control studies • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies, nonoriginal data (e.g., narrative reviews, scoping reviews, editorials, letters, or erratum), retrospective cohort studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., nonlongitudinal) studies, survey
Publications	• Studies published in English only • Studies published in peer-reviewed journals • Studies published at and after the year 2000	• Non-English language studies

Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal; HDL = high-density lipoprotein; KQ = Key Question; LDL = low-density lipoprotein PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; TC = total cholesterol; U.S. = United States

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

We plan to conduct a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to the present. We have developed a preliminary database search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search U.S. Food and Drug Administration (FDA), ClinicalTrials.gov, Health Canada, U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X9; Thomson Reuters, Philadelphia, PA). In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal will be available to collect additional study-specific information from industry stakeholders, professional societies, and researchers. A Federal Register Notice will be posted for this review.

For abstract screening, we plan to use a validated Natural Language Processing (NLP) algorithm developed by DistillerSR® (Evidence Partners Incorporated, Ottawa, Canada). Each abstract will be screened by one human reviewer and the NLP technique with constant surveillance of possible misclassified citations for quality control. Consensus for inclusion and conflicts will be advanced for full-text screening. Independent reviewers, working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus cannot be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

C. Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (e.g., author, year, study design, inclusion and exclusion criteria, patient characteristics(e.g., age, sex, race/ethnicity, country), intervention, comparisons,

outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will review data extraction and resolve conflicts. In case the included studies do not report all necessary information (e.g., methods and results), we will contact authors directly. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

D. Assessment of the Risk of Bias of Individual Studies

We will evaluate the risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias 2 tool[32] to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For nonrandomized studies, including quasi-experimental studies, controlled before-and-after studies, prospective cohort studies, and nested case-control studies, we will use the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool.[33] In addition, we will report funding source of the included studies.

E. Data Synthesis

We will qualitatively summarize key features/characteristics (e.g., study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for the KQ.

We will determine whether a meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If meta-analysis is deemed appropriate, we plan to use random-effects models to pool estimates from the included studies. We will evaluate heterogeneity between studies using I^2 indicator.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests, such as the Egger linear regression test if the number of studies included in a direct comparison is large ($n \geq 10$).

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of the body of evidence (SOE) per the EPC methods guide on assessing SOE.[34] We will grade SOE for end outcomes, including cardiovascular disease, stroke, and cardiovascular disease-related mortality. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

RCTs start as high SOE. [34] The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias), precision (based on the size of the body of evidence, number of events, and confidence intervals), directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates),consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity), and the likelihood of reporting and publication bias.

We will lower the SOE grading when the majority of studies in a particular comparison have high or unclear risk of bias or when sensitivity analyses show a substantial difference in estimates derived from high or unclear risk of bias studies versus estimates derived from studies at low risk of bias. If a sufficient body of evidence can be derived from low risk of

bias studies, we may exclude high and unclear risk of bias studies and not rate down the SOE. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign the SOE rating as high, moderate, low, or insufficient evidence to estimate an effect

High: We are very confident that the estimate of effect lies close to the true effect (i.e., the body of evidence has few or no deficiencies and is judged to be stable).

Moderate: We are moderately confident that the estimate of effect lies close to the true effect (i.e., the body of evidence has some deficiencies and is judged to be likely stable).

Low: We have limited confidence that the estimate of effect lies close to the true effect (i.e., the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient - We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

We will produce summary of evidence tables that will provide the following for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

G. Assessing Applicability

Applicability is limited to the general population.

IV. References

1. de Fatima Marinho de Souza M, Gawryszewski VP, Ordunez P, et al. Cardiovascular disease mortality in the Americas: current trends and disparities. Heart. 2012 Aug;98(16):1207-12. doi: 10.1136/heartjnl-2012-301828. PMID: 22826558.

2. Manemann SM, Gerber Y, Bielinski SJ, et al. Recent trends in cardiovascular disease deaths: a state specific perspective. BMC Public Health. 2021 Jun 1;21(1):1031. doi: 10.1186/s12889-021-11072-5. PMID: 34074276.

3. Mensah GA, Wei GS, Sorlie PD, et al. Decline in Cardiovascular Mortality: Possible Causes and Implications. Circ Res. 2017 Jan 20;120(2):366-80. doi: 10.1161/CIRCRESAHA.116.309115. PMID: 28104770.

4. Ahmad FB, Anderson RN. The Leading Causes of Death in the US for 2020. JAMA. 2021 May 11;325(18):1829-30. doi: 10.1001/jama.2021.5469. PMID: 33787821.

5. Mohebi R, Chen C, Ibrahim NE, et al. Cardiovascular Disease Projections in the United States Based on the 2020 Census Estimates. J Am Coll Cardiol. 2022 Aug 9;80(6):565-78. doi: 10.1016/j.jacc.2022.05.033. PMID: 35926929.

6. World Health Organization. Prevention of cardiovascular disease : guidelines for assessment and management of total cardiovascular risk. World Health Organization. 2007.

7. National Health and Medical Research Council. Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes,. 2006.

8. EFSA Panel on Dietetic Products N, and Allergies (NDA);. Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre. EFSA Journal 2010;8(3).

9. Food Safety Authority of Ireland. Scientific Recommendations for Healthy Eating Guidelines in Ireland. 2011.

10. Scientific Advisory Committee on Nutrition. Carbohydrates and Health. In: England PH, editor; 2015.

11. Trumbo P, Schlicker S, Yates AA, et al. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc. 2002 Nov;102(11):1621-30. doi: 10.1016/s0002-8223(02)90346-9. PMID: 12449285.

12. World Health Organization. Diet, nutrition and the prevention of chronic diseases. Report of a joint WHO/FAO expert consultation. In: World Health Organization, editor; 2003.

13. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015.; 2015.

14. Buyken AE, Mela DJ, Dussort P, et al. Dietary carbohydrates: a review of international recommendations and the methods used to derive them. Eur J Clin Nutr. 2018 Dec;72(12):1625-43. doi: 10.1038/s41430-017-0035-4. PMID: 29572552.

15. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press; 2005.

16. Jo U, Park K. Carbohydrate Intake and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis of Prospective Studies. Nutrients. 2023 Apr 2;15(7). doi: 10.3390/nu15071740. PMID: 37049580.

17. Qin P, Huang C, Jiang B, et al. Dietary carbohydrate quantity and quality and risk of cardiovascular disease, all-cause, cardiovascular and cancer mortality: A systematic review and meta-analysis. Clin Nutr. 2023 Feb;42(2):148-65. doi: 10.1016/j.clnu.2022.12.010. PMID: 36586217.

18. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017 Nov 4;390(10107):2050-62. doi: 10.1016/S0140-6736(17)32252-3. PMID: 28864332.

19. Mohammadifard N, Mansourian M, Firouzi S, et al. Longitudinal association of dietary carbohydrate and the risk cardiovascular disease: a dose-response meta-analysis. Crit Rev Food Sci Nutr. 2022;62(23):6277-92. doi: 10.1080/10408398.2021.1900057. PMID: 33739217.

20. Hu T, Jacobs DR, Bazzano LA, et al. Low-carbohydrate diets and prevalence, incidence and progression of coronary artery calcium in the Multi-Ethnic Study of Atherosclerosis (MESA). Br J Nutr. 2019 Feb 28;121(4):461-8. doi: 10.1017/S0007114518003513. PMID: 30630542.

21. Song S, Song WO, Song Y. Dietary carbohydrate and fat intakes are differentially associated with lipid abnormalities in Korean adults. J Clin Lipidol. 2017 Mar-Apr;11(2):338-47 e3. doi: 10.1016/j.jacl.2017.01.016. PMID: 28502489.

22. Mente A, Dehghan M, Rangarajan S, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. Lancet Diabetes Endocrinol. 2017 Oct;5(10):774-87. doi: 10.1016/S2213-8587(17)30283-8. PMID: 28864143.

23. Ma Y, Li Y, Chiriboga DE, et al. Association between carbohydrate intake and serum lipids. J Am Coll Nutr. 2006 Apr;25(2):155-63. doi: 10.1080/07315724.2006.10719527. PMID: 16582033.

24. Ford ES, Liu S. Glycemic index and serum high-density lipoprotein cholesterol concentration among us adults. Arch Intern Med. 2001 Feb 26;161(4):572-6. doi: 10.1001/archinte.161.4.572. PMID: 11252117.

25. Jovanovski E, de Castro Ruiz Marques A, Li D, et al. Effect of high-carbohydrate or high-monounsaturated fatty acid diets on blood pressure: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2019 Jan 1;77(1):19-31. doi: 10.1093/nutrit/nuy040. PMID: 30165599.

26. Shah M, Adams-Huet B, Bantle JP, et al. Effect of a high-carbohydrate versus a high--cis-monounsaturated fat diet on blood pressure in patients with type 2 diabetes. Diabetes Care. 2005 Nov;28(11):2607-12. doi: 10.2337/diacare.28.11.2607. PMID: 16249527.

27. Appel LJ, Sacks FM, Carey VJ, et al. Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 2005 Nov 16;294(19):2455-64. doi: 10.1001/jama.294.19.2455. PMID: 16287956.

28. Schwingshackl L, Chaimani A, Schwedhelm C, et al. Comparative effects of different dietary approaches on blood pressure in hypertensive and pre-hypertensive patients: A systematic review and network meta-analysis. Crit Rev Food Sci Nutr. 2019;59(16):2674-87. doi: 10.1080/10408398.2018.1463967. PMID: 29718689.

29. Zazpe I, Santiago S, Gea A, et al. Association between a dietary carbohydrate index and cardiovascular disease in the SUN (Seguimiento Universidad de Navarra) Project. Nutr Metab Cardiovasc Dis. 2016 Nov;26(11):1048-56. doi: 10.1016/j.numecd.2016.07.002. PMID: 27524801.

30. Ludwig DS, Hu FB, Tappy L, et al. Dietary carbohydrates: role of quality and quantity in chronic disease. BMJ. 2018 Jun 13;361:k2340. doi: 10.1136/bmj.k2340. PMID: 29898880.

31. AlEssa HB, Cohen R, Malik VS, et al. Carbohydrate quality and quantity and risk of coronary heart disease among US women and men. Am J Clin Nutr. 2018 Feb 1;107(2):257-67. doi: 10.1093/ajcn/nqx060. PMID: 29529162.

32. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.

33. ROBINS-E Development Group (Higgins J MR, Rooney A, Taylor K, Thayer K, Silva R, Lemeris C, Akl A, Arroyave W, Bateson T, Berkman N, Demers P, Forastiere F, Glenn B, Hróbjartsson A, Kirrane E, LaKind J, Luben T, Lunn R, McAleenan A, McGuinness L, Meerpohl J, Mehta S, Nachman R, Obbagy J, O'Connor A, Radke E, Savović J, Schubauer-Berigan M, Schwingl P, Schunemann H, Shea B, Steenland K, Stewart T, Straif K, Tilling K, Verbeek V, Vermeulen R, Viswanathan M, Zahm S, Sterne J). Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). ROBINS-E tool; 2023.

34. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

V. Definition of Terms

AHRQ	Agency for Healthcare Research and Quality
AI	Adequate Intake
CVD	Cardiovascular Disease
DRI	Dietary Reference Intake

FDA	Food and Drug Administration
HDL	High-density Lipoprotein
KQ	Key Questions
LDL	Low-density Lipoprotein
MHRA	Medicines and Healthcare Products Regulatory Agency
NLP	Natural Language Processing
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design
RDA	Required Daily Allowance
ROBINS-E	Risk Of Bias In Non-randomized Studies - of Exposure
SEADS	Supplemental Evidence and Data for Systematic Reviews
SOE	Strength of Evidence
TC	Total Cholesterol
TEP	Technical Expert Panel
TOO	Task Order Officer
U.K.	United Kingdom
U.S.	United States

VI. Summary of Protocol Amendments

If the EPC needs to amend the protocol, the EPC will provide the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol.

VII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel (TEP) is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and 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 suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 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 AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or

editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

IX. 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. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

X. Role of the Funder

This project was funded under Contract No. 75Q80120D00005 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to 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 either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XI. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).