

Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Treatment for Hepatitis C in Adults

I. Background and Objectives

Objective

The stated objective of our systematic review is to evaluate the comparative effectiveness of treatment for hepatitis C.

Summary of Nomination

Based on a 2004 systematic review of the evidence for screening for hepatitis C virus (HCV) infection, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against routine screening in adults at high risk for infection.^{1,2} However, the review did support the effectiveness of treatment for HCV infection within the context of risk assessment and screening in the general population. The current topic was nominated by several organizations interested in both updating the existing recommendation related to screening and expanding the scope to include broader elements of treatment such as the comparative effectiveness of several new classes of drugs and interventions to improve adherence to treatment.

The issue of adherence to antiviral treatment and outcomes was considered and discussed by AHRQ. Due to the complexity of these issues, three separate but complementary reviews will be conducted and will focus respectively on HCV screening, HCV treatment, and adherence to HCV antiviral therapy.

This review defines the methods used to address the comparative effectiveness of antiviral treatment with the level of detail suggested by the key informants, including the comparative effectiveness of treatments between patient subgroups (by race, genotype, age, sex, disease severity, etc.); effects of dose and duration of therapy; and benefits and harms of different combinations of drug treatment, including the recently approved protease inhibitors, telaprevir³ and boceprevir.⁴

Background and Clinical Context

HCV is the most common chronic blood-borne pathogen in the United States; infection with HCV is usually chronic. The virus is primarily transmitted through percutaneous exposure to blood, with the most common risk factors being intravenous drug use, multiple sexual partners and sexual contact with an HCV-infected person. The prevalence of HCV infection in the U.S. is estimated to be 1.6 percent, with a peak of 4.3 percent in people 40 to 49 years of age.⁵ Approximately 78 percent of those who test positive for anti-HCV antibody have chronic HCV infection.⁵ The Centers for Disease Control and Prevention (CDC) estimates that there were 17,000 new cases of HCV infection in 2007.⁶ Infection with HCV is a leading cause of chronic

liver disease in the US, with the direct medical costs of HCV-related liver disease projected to reach \$10.7 billion by the year 2019.⁷ The CDC estimates that 60 to 70 percent of HCV-infected adults are asymptomatic.⁶

The treatment of HCV infection has evolved dramatically over the past two decades. The current standard antiviral medication treatment for HCV infection is pegylated interferon combined with ribavirin. Previous reviews have found insufficient evidence to favor either pegylated interferon alfa-2a or pegylated interferon alfa-2b.^{8,9} While the goals of treatment are to prevent the long-term health complications associated with HCV infection such as cirrhosis and liver cancer, clinical trials are never long enough to provide direct evidence related to these outcomes. Because of this viral kinetics have become important predictors of long-term prognosis in patients with HCV. Most notably, sustained virologic response (SVR), commonly defined as a decline in HCV RNA to undetectable levels 24 weeks following treatment completion, is considered the standard marker of successful treatment because it is strongly associated with continued freedom from viremia as well as reductions in mortality, liver failure, and cancer.¹⁰⁻¹³ Combination treatment with a pegylated interferon and ribavirin has been shown to achieve SVR in about 55 percent of patients.

However, variety of factors may be associated with different responses to treatment, complicating treatment decisions. Among these factors is HCV genotype, with higher SVR rates in patients with genotypes 2 or 3 (SVR of 70 to 80 percent) compared with those with genotype 1 (SVR of 40 to 50 percent).^{14,15} Another factor that may be associated with SVR is disease severity, as measured by viral load, elevated ALT levels, and/or the presence of bridging fibrosis or cirrhosis on liver biopsy.¹⁴ Some evidence suggests that host factors such as female gender, age less than 40 years, and non-African-American race may be associated with more favorable responses to antiviral treatment.¹⁵ In addition, recent findings that a set of polymorphisms in the region of the interleukin-28B (IL28B) gene were positively associated with higher SVR¹⁵ suggest the potential for using genetic markers in predicting treatment response and refining treatment regimens. In consideration of factors associated with different response rates, guidelines for treatment suggest different dosages and durations of treatment according to various factors.¹⁰ A common (50 to 60 percent) adverse effect of treatment with interferon and ribavirin is an influenza-like syndrome that can have a substantial effect on quality of life due to the usually long duration (approximately 6 months) of treatment. In addition, psychiatric, gastrointestinal, dermatological, and hematologic adverse effects underlie high treatment discontinuation rates.⁸ As such, it is important for clinicians to consider multiple viral and host characteristics when deciding to initiate antiviral treatment. A better understanding of viral factors, host factors, differences in medication dosing and duration, and the interplay of these elements would be useful for clinical decisionmaking.

This review will assess the comparative effectiveness of pegylated interferon alfa-2a and pegylated interferon alfa-2b, each combined with ribavirin, in adults with HCV infection. The recently FDA approved protease inhibitors^{3,4} will also be included (e.g., telaprevir and boceprevir) and head-to-head comparisons with the current standard of therapy (pegylated interferon alfa-2a or pegylated interferon alfa-2b) will also be evaluated. Intermediate outcomes, such as viremia and histologic changes, and ultimate health outcomes, such as mortality and morbidity from HCV infection, will be assessed. A 2004 review for the USPSTF found only fair quality evidence linking improvement in intermediate outcomes with ultimate health outcomes.^{1,2}

and a feasibility scan of the literature identified a number of relevant studies published since the previous review addressing this key question. An additional consideration is the variability in sustained viral response (SVR) between different HCV genotypes and differences in duration and dosing and the comparative effectiveness of different treatment regimens among various patient subgroups defined by the characteristics discussed below.

Input from Key Informants: Review of Hepatitis C Treatments

During the topic refinement process, discussions with Key Informants led us to revise the nominated topic and conduct a separate but complementary review, the Comparative Effectiveness of Treatment for Hepatitis C. Key Informants discussed the importance of a thorough understanding of the comparative effectiveness of treatment for HCV infection, emphasizing the variability in treatment between patient subgroups, including the interaction of some subgroup characteristics with race and HCV genotype. Key questions were also posted to the AHRQ website for public comment, but this input did not result in substantial changes to the questions.

II. Key Questions and Population, Intervention, Comparator(s), Outcome(s), Timing and Setting(s) [PICOTS]

Key Questions

Question 1

What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?

- a. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Question 2

What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?

- a. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Question 3

What are the comparative harms associated with antiviral treatments?

- a. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

Question 4

Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

PICOTS Criteria

Population(s):

- Non-co-infected adults with HCV infection who have not had previous antiviral drug treatment
- Subgroups included: HCV genotype (e.g., genotype 1 or 4 vs. 2 or 3); race (e.g., black vs. non-black); sex; stage of disease (e.g., cirrhosis or fibrosis); others (e.g., baseline viral load, weight)
- Exclusions: pregnant women, HIV co-infection, transplant recipients, and patients with renal failure

Interventions:

- Pegylated interferon alfa-2a with ribavirin
- Pegylated interferon alfa-2b with ribavirin
- Protease inhibitors (e.g., telaprevir, boceprevir)

Comparators:

- One antiviral treatment versus another
- Comparisons between different doses of antiviral therapy and dosing protocols
- Comparisons between different durations of antiviral therapy and different methods for guiding duration therapy (e.g., fixed-duration vs. response-guided duration)

Outcomes:

Intermediate outcomes

- Sustained virological response (SVR) rates
- Histological changes

- Behavioral changes to improve health outcomes and reduce HCV transmission

Final outcomes

- Morbidity and mortality from HCV, including quality of life, hepatic cirrhosis, hepatocellular carcinoma, and liver transplants
- Transmission of HCV

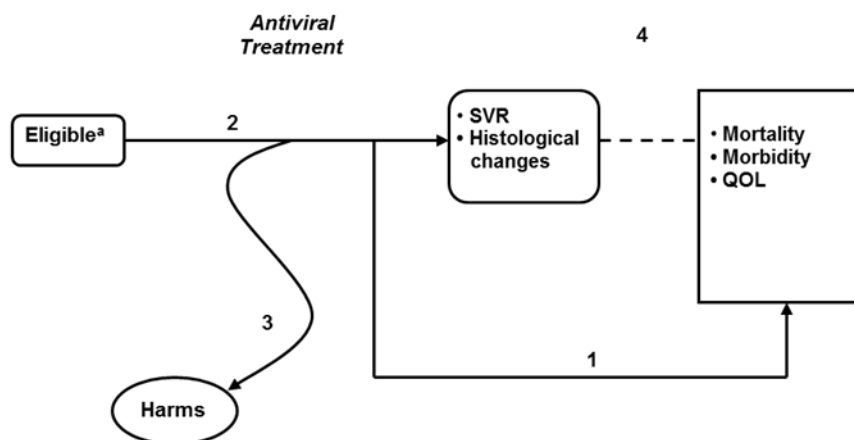
Adverse effects of intervention(s)

- Harms from antiviral treatment, including withdrawals due to adverse events, serious adverse events such as severe neutropenia, psychological adverse events, flu-like symptoms, and hematological adverse events

Timing and Setting:

No minimum timing and all settings included.

III. Analytic Framework



^aRefers to eligibility for antiviral treatment based on viral and host factors.

Abbreviations: QOL = quality of life; SVR = sustained virological response

IV. Methods

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

Literature included will meet the PICOTS outlined above and the review will include observational studies, systematic reviews, and clinical trials (case studies and small case series)

Source: www.effectivehealthcare.ahrq.gov

Published Online: November 30, 2011

are excluded). Non-English language articles will be included in this review and translated when it is feasible.

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

Results from previously conducted meta-analyses and systematic reviews on these topics will be sought and used where appropriate and updated when necessary. In addition to using MEDLINE® to identify systematic reviews, a research librarian will search the Cochrane Databases of Systematic Reviews and Controlled Trials and Database of Abstracts of Reviews of Effectiveness.

To identify articles relevant to each Key Question (KQ), the librarian will search the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, Evidence-Based Medicine Reviews (EBMR) and Ovid MEDLINE® (see Table 1: Example Search Strategy). We will search all electronic bibliographies from 1947 to present. Grey literature will be identified by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries), grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD) and the Web sites of individual funders. Scientific Information Packets will be solicited from industry stakeholders through the Scientific Resource Center.

Abstracts and full-text articles will be reviewed in duplicate for inclusion and exclusion for each KQ. After finalizing literature searches, the research team will review titles and abstracts using pre-established inclusion/exclusion criteria to determine potential eligibility for inclusion in the evidence synthesis. All citations that are judged to meet the inclusion criteria by at least one reviewer will be retrieved for full text review.

All retrieved studies will be reviewed in duplicate. Data will be extracted from studies meet our inclusion criteria entered into an electronic database. A consensus process will be used to arbitrate conflicting assignments of eligibility and ineligibility, and a file of excluded studies with reasons for the exclusion of each will be maintained. Searches will be updated while the report is posted for public comment and peer review to capture new publications. Literature identified during the updated search will go through the same process of dual review as all other studies considered for inclusion in the report. If any pertinent new literature is identified for inclusion in the report, it will be incorporated before the report is finalized.

Table 1. Sample search strategy

Concept	Search String	N
1: Hepatitis C	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp	51104
2: Treatment	Antiviral agents/ OR Interferons/ OR Interferon-alpha/ OR Interferon Alfa-2a/ OR Interferon Alpha-2b/ OR Interferon\$.mp OR interferon alpha-2a.mp OR interferon alpha-2b.mp OR IFNalpha2a.mp OR IFNalpha2b.mp OR interferon alpha 2a.mp OR interferon alpha 2b.mp OR Exp Polyethylene Glycols/ OR pegasys.mp OR Peg-intron.mp OR peginterferon alpha-2a.mp OR peginterferon alpha-2b.mp OR peginterferon alpha 2a.mp OR peginterferon alpha 2b.mp OR pegylated interferon\$.mp OR IFN\$.mp OR PEG IFN\$.mp OR Ribavirin/ OR ribavirin.mp OR RBV.mp OR Exp Protease Inhibitors/ OR protease inhibitor\$.mp OR polymerase inhibit\$.mp OR HCV protease\$.mp OR	347804

Source: www.effectivehealthcare.ahrq.gov

Published Online: November 30, 2011

	telaprevir.mp OR boceprevir.mp	
Hepatitis C and treatment	1 AND 2	15019
Methods Limit	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti.ab	5185
Further Limits: Adult (19-44), Middle Age (45-64), All Aged (65+) publication date = 2002-current		1178

C. Data Abstraction and Data Management

The following data will be extracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, hepatitis C treatments and comparisons, the method of outcome ascertainment if available and results for each outcome. An investigator will extract study data and a second investigator will review extractions. Intention-to-treat (ITT) results will be recorded if available.

D. Assessment of Methodological Risk of Bias of Individual Studies

The risk of bias of systematic reviews, randomized trials, and cohort and case control studies will be assessed based on predefined criteria. Criteria from the Assessment of Multiple Systematic Reviews (AMSTAR) tool (systematic reviews), methods proposed by Downs and Black (observational studies),¹⁶ and methods developed by the US Preventive Services Task Force¹⁷ will be adapted to assess the risk of bias. Results from high risk of bias studies will most likely be excluded from data syntheses, though these data will still be included in evidence tables. All risk of bias assessments will be completed by two independent investigators and disagreements reconciled by consensus. The criteria we will use are consistent with the approach recommended by AHRQ in the prepublication draft of the *Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).¹⁸

Systematic Reviews

Included systematic reviews will also be rated for risk of bias based on pre-defined criteria assessing whether they had a clear statement of the questions(s), reported inclusion criteria, used an adequate search strategy, assessed validity, reported adequate detail of included studies, and used appropriate methods to synthesize the evidence.¹⁹

Trials

The internal validity of each trial will be assessed based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories will be rated high risk of bias; trials that met all criteria will be rated low risk of bias; the remainder will be rated moderate risk of bias. As the “moderate risk of bias” category is broad, studies with this rating vary in their strengths and

weaknesses: the results of some moderate risk of bias studies are *likely* to be valid, while others are only *probably* valid. A “high risk of bias” trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared interventions.

Observational Studies

For assessing the internal validity of observational studies, the following will be evaluated: whether they used nonbiased selection methods; whether rates of loss to follow-up were acceptable; whether pre-defined outcomes were specified; whether they used appropriate methods for ascertaining exposures, potential confounders, and outcomes; and whether they performed appropriate statistical analyses of potential confounders. Although many tools exist for quality assessment of nonrandomized trials, there is no consensus on optimal rating methods;²⁰ therefore, no formal scoring system to assess the risk of bias in observational studies will be used, though methodological deficiencies will be noted in any of the above areas when present.

E. Data Synthesis

Evidence tables will be constructed to show study characteristics and risk-of-bias ratings for all included studies. To determine the appropriateness of meta-analysis, the clinical and methodological diversity and assessed statistical heterogeneity will be considered. Appropriate measures will be chosen based on the type of data for meta-analysis. We will use standard χ^2 tests to assess the presence of statistical heterogeneity among studies, and the I^2 statistic to test the magnitude of heterogeneity. When appropriate, we will use a random effects model to combine studies while accounting for variation among studies. We will use a fixed effects model to combining rare binary outcomes. When there is no variation among studies, the random effects model yields the same results as a fixed effects model. Statistical heterogeneity will be explored by using subgroup analysis or meta-regression.

When statistical meta-analysis is not possible, we will group studies by similarity of intervention characteristics and plot trends in the study findings. Where possible, we will group similar outcome measures across the studies to make preliminary estimates of effect sizes. Direct comparisons will be made when head-to-head trials are available. Otherwise, indirect comparisons will be considered if the outcome measures for nonintervention are similar across the studies evaluated. We will also assess differences in treatment effect or harm in relevant subgroups stratified by race, HCV genotype, weight, and baseline HCV viral level.

F. Grading the Evidence for Each Key Question

We will use the methods outlined in Chapter 10 of the AHRQ *Methods Guide*¹⁸ to grade strength of evidence. (An edited version of the chapter has also been published in the *Journal of Clinical Epidemiology*.²⁰) Domains considered in grading the strength of evidence include consistency, directness, precision and risk of bias. Based on this assessment, the body of evidence will be assigned a strength-of-evidence grade of high, moderate, or low. In cases where

evidence does not exist, is sparse, or contains irreconcilable inconsistency, a grade of insufficient evidence will be assigned.

G. Assessing Applicability

Because this review addresses a treatment-naïve population, this review is not applicable to those who failed previous therapies or are nonresponders. Also, this review is not applicable to patients who are co-infected with HIV. The applicability of studies will be assessed in terms of the degree to which the study population, interventions, outcomes, and settings are relevant to individuals who would be considered for hepatitis C treatment and features that may affect the effectiveness of the intervention such as genotype and study country.

V. Definition of Terms

Not applicable.

VI. References

1. Chou R, Clark EC, Helfand M, for the US Preventive Services Task Force. Screening for hepatitis C virus infection: a review of the evidence for the US Preventive Services Task Force. *Ann Intern Med* 2004 Mar 16;140(6):465-79. PMID: 15023713.
2. US Preventive Services Task Force Web site. Screening for Hepatitis C in Adults: Recommendation Statement. March 2004. Available at: <http://www.uspreventiveservicestaskforce.org/uspstf/uspshcpc.htm>. Accessed November 10, 2010.
3. US Food and Drug Administration. FDA approves Incivek for hepatitis C. FDA News Release; May 23, 2011. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm256299.htm>. Accessed November 9, 2011.
4. US Food and Drug Administration. FDA approves Victrelis for hepatitis C. FDA News Release; May 13, 2011. Available at: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm255390.htm>. Accessed November 9, 2011.
5. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006 May 16;144(10):705-14. PMID: 16702586.
6. Centers for Disease Control and Prevention. The ABCs of hepatitis. Atlanta, GA: US Department of Health and Human Services; June 2010. Publication No. 21-1076. Available at: <http://www.cdc.gov/hepatitis/Resources/Professionals/PDFs/ABCTable.pdf>. Accessed November 9, 2011.
7. Wong JB, McQuillan GM, McHutchison JG, et al. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000 Oct;90(10):1562-9. PMID: 11029989.

8. Chou R, Carson S, Chan BKS, Care B. *Drug Class Review on Pegylated Interferons for Hepatitis C*. 2007. Available: <http://www.ohsu.edu/drugeffectiveness/reports/final.cfm>. Accessed :January 24, 2010.
9. Awad T, Thorlund K, Hauser G, Stimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alpha-2b in chronic hepatitis C: systematic review of randomized trials. *Hepatology* 2010 Apr; 51(4):1176-1184. PMID: 20187106.
10. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clin Gastroenterol Hepatol*. 2011 Jun;9(6):509-516.e1. Epub 2011 Mar 11. PMID: 21397729.
11. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. *Ann Intern Med* 2007 Nov 20;147(10):677-84. PMID: 18025443.
12. Cardoso AC, Moucari,R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010 May;52(5)652–7. Epub 2010 Mar 4. PMID: 20346533.
13. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. *Gastroenterology* 2010;139:1593–1601. PMID: 20637202.
14. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management and treatment of hepatitis C: an update. *Hepatology*. 2009 Apr;49(4):1335-1374. PMID: 19330875.
15. Afdhal, NH, McHutchison, JG, Zeuzem, S, et al. Hepatitis C pharmacogenetics: state of the art in 2010. *Hepatology*, 53 Jan;53(1):336–345. doi: 10.1002/hep.24052. PMID: 21254181.
16. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*, 1998 Jun; 52(6):377–384. PMID: 9764259.
17. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
18. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality, August 2011. Chapters available at: <http://www.effectivehealthcare.ahrq.gov>. Accessed November 9, 2011.
19. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomized intervention studies. *Health Technol Assess*. 2003;7(27):iii-x, 1-173. PMID: 14499048.
20. Owens DK, Lohr KN, Atkins D et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health Care Program. *J Clin Epidemiol* 2010;63(5)513-23. PMID: 19595577.

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.

VII. Review of Key Questions

For all EPC reviews, key questions are 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. In addition, for Comparative Effectiveness reviews, the key questions are posted for public comment and finalized by the EPC after review of the comments.

VIII. 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 healthcare 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 TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Expert Panel (TEP)

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic 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 healthy 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.

XI. Peer Review

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.