Effective Health Care

Hepatitis C Treatment

Results of Topic Selection Process & Next Steps

The nominator, American Academy of Family Physicians (AAFP) is interested in using a new systematic review to inform a new AAFP clinical practice guideline for primary care physicians on antiviral treatment for hepatitis C virus (HCV) infection. This topic meets all criteria but was not funded. Due to limited program resources, the program is unable to develop a review at this time. No further activity on this topic will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Chronic Hepatitis C Treatment, #0696

Nomination Date: 07/08/2017

Topic Brief Date: 09/20/2017

Authors:
Laura Pincock
Christine Chang

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: This topic is both appropriate and important, representing a significant disease burden for a large part of the population.
- Duplication: A new review on this topic would not be duplicative of an existing product. While available reviews cover key portions of the scope, few reviews have systematically reviewed the evidence on clinical outcomes and two new direct-acting antiviral regimens have been recently approved by the FDA.
- Impact: Most guidance from Federal sources and others refer to the AASLD/IDSA guidelines on Hepatitis C treatment from April 2017. With the proliferation of new drug regimens, an updated review looking across treatment options is needed.
- Feasibility: A new review may be feasible. However there are a few studies comparing one direct-acting antiviral (DAA) combination regimen to another; most studies were short-term and looked at sustained viral response for 12 or more weeks (SVR12); and a few studies looked at clinical outcomes. There are many studies in the pipeline, so it is anticipated that additional studies directly comparing DAA regimens may become available in the future.
- Value: This review would be potentially useful to multiple stakeholder groups. The rise in Hepatitis C infection is tied to the opioid crisis, and could inform and complement efforts by Federal agencies.

Table of Contents

Introduction

An estimated 2.7 million individuals in the U.S. are chronically infected with HCV. Due to the high proportion of persons who were infected in the 1960s and 1970s, the burden of HCV infection and its consequences (cirrhosis, hepatocellular cancer, premature death, etc.) are expected to increase in the coming decades. Expanded screening and effective interferon-free treatment regimens that can be safely prescribed in primary care settings have the potential to substantially reduce the public health burden of HCV infection over the coming years. The Project ECHO (Extension for Community Healthcare Outcomes) model tested in New Mexico, Arizona, and Utah demonstrated that with appropriate training, HCV infection treatment managed by a primary care clinician produced similar outcomes as treatment managed by an infectious disease or gastrointestinal subspecialists. However, as most family physicians do not have direct experience prescribing antiviral medications for patients with HCV infection, they may feel ill-prepared to respond to the increasing demand for treatment. Updating AHRQ's 2012 evidence report on antiviral treatments for HCV infection would provide crucial and timely guidance for primary care physicians.

Nominator and Stakeholder Engagement: AAFP has a long-standing relationship with AHRQ and the EHC program. The AAFP consistently uses evidence reports produced by this program to develop clinical practice guidelines.

Topic nomination #0696 was received on July 8, 2016. It was nominated by AAFP. The questions for this nomination are:

Key Question 1. What is the comparative effectiveness of antiviral treatment in improving morbidity and mortality in patients with HCV infection? How does the effectiveness of antiviral treatment vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

Key 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? 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?

Key Question 3. What are the comparative harms associated with antiviral treatments? Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 4. How well do improvements in intermediate outcomes (SVR, histologic changes) predict reduced morbidity and mortality in patients with HCV infection?

Key Question 5. Are there clinically significant differences in intermediate and health outcomes of antiviral treatment managed by primary care providers versus subspecialists?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, and setting (PICOS) of interest. See Table 1.

Table 1. Key Questions and PICOS

Key Questions	What is the comparative effectiveness of antiviral treatment in improving morbidity and mortality in patients with chronic HCV infection?	What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?	What are the comparative harms associated with antiviral treatments?	How well do improvements in intermediate outcomes (SVR, histologic changes) predict reduced morbidity and mortality in patients with HCV infection?	Are there clinically significant differences in intermediate and health outcomes of antiviral treatment managed by primary care providers versus subspecialists?
Population	Non-co-infected adults with chronic HCV infection who have not had previous antiviral drug treatment Subgroups include: • 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	Non-co-infected adults with chronic HCV infection who have not had previous antiviral drug treatment Subgroups include: • 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	Non-co-infected adults with chronic HCV infection who have not had previous antiviral drug treatment Subgroups include: • 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		Non-co-infected adults with chronic HCV infection who have not had previous antiviral drug treatment
Interventions	Direct acting antiviral (DAA) combination therapy	Direct acting antiviral (DAA) combination therapy	Direct acting antiviral (DAA) combination therapy		Management by primary care clinician
Comparators	Other DAA combination therapy	Other DAA combination therapy	Other DAA combination therapy		Management by specialty care clinician
Outcomes	HCC, mortality, cirrhosis, need for liver transplantation, quality of life, viral resistance to therapy	Sustained viral response, histologic changes in the liver (inflammation, fibrosis)	Anemia, psychological adverse events, withdrawals due to adverse events, flu-like symptoms, HCC, etc.		Clinical and intermediate outcomes, quality of life
Setting	Outpatient	Outpatient	Outpatient		Outpatient

Abbreviations:
hepatocellular carcinoma (HCC), hepatitis C virus (HCV); sustained virologic response (SVR), direct acting antiviral (DAA) therapy, human immunodeficiency virus (H

Methods

To assess topic nomination Hepatitis C Treatment for priority for a systematic review or other AHRQ EHC report, we used a hierarchical process based on established criteria. Findings of each assessment determined the need for further evaluation. Details are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Appendix B includes the list of the sources.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was hypothetically possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed for the past 5 years, up to 9/27/2017. In addition, for all topics, we searched ClinicalTrials.gov for in-process or recently completed unpublished studies.

We identified and reviewed 218 abstracts and titles \for inclusion and classified included studies by study design, to assess the size and scope of a potential systematic review.

Value

We assessed the nomination for value (see Appendix A). We considered whether or not the topic would inform clinical policy in community and/or clinical settings, and if there was a partner organization that would use this evidence review to do disseminate this policy.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic, representing a significant disease burden for a large part of the population.

Desirability of New Review/Duplication

A new evidence review examining hepatitis C would not be duplicative of an existing product. Available reviews cover key portions of the scope and few reviews have systematically reviewed the evidence on clinical outcomes. In addition, two new direct-acting antiviral regimens have been recently approved by the FDA and are not involved in existing reviews

Impact of a New Evidence Review

Most guidance from Federal sources and others refer to the AASLD/IDSA guidelines on Hepatitis C treatment which was released in April 2017. However, two new regimens were FDA-approved in recent months. With the proliferation of new drug regimens, an updated review looking across treatment options is needed.

Feasibility of a New Evidence Review

A new review may be feasible. Scoping of the review and including concerns from other perspectives could broaden the scope and increase the number of relevant studies. There are a few studies comparing one direct-acting antiviral (DAA) combination regimen to another. Most studies compare the same DAA regimen with immediate vs. deferred timing of therapy, the same 2-3 drug base regimen with or without the addition of ribavirin, or the regimen may include previous or current interferon. Most studies were short-term and looked at sustained viral response for 12 or more weeks (SVR12). Only a few studies looked at clinical outcomes. There are many studies in the pipeline, so it is anticipated that additional studies directly comparing DAA regimens may become available in the future.

- If the scope focused only on head-to-head comparisons of DAAs (as described in this brief) the scope would be small.
- If the scope were broadened to include comparators other than DAAs, the estimated scope would be large.

See Table 2, Feasibility column for the citations that were determined to address the key questions.

Table 2. Results of Duplication and Feasibility Searches

Key Question	Duplication (Completed or In-Process Evidence Reviews, 9/2014-9/2017)	Feasibility (Published and Ongoing Research, September 2012-9/27/2017)
KQ 1: What is the comparative effectiveness of antiviral treatment in **improving morbidity and mortality** in patients with chronic HCV infection?	Total number of identified systematic reviews: 1 • Completed SR-1 (Cochrane)[22]	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov • Recruiting: #2 [23,31] • Active: #3[24,26,52] • Complete: #5[25,27-30]

Key Question	Duplication (Completed or In-Process Evidence Reviews, 9/2014-9/2017)	Feasibility (Published and Ongoing Research, September 2012-9/27/2017)
KQ 2: What is the comparative effectiveness of antiviral treatments on **intermediate outcomes, such as the rate of SVR or histologic changes in the liver**?	Total number of identified systematic reviews: 5 • Completed SR by genotype-1[1, 24] • Completed SR on race-1[2] • Completed SR some exclusions-2[3-4]	Size/scope of review Relevant Studies Identified:5 ○ Retrospective study-1[15] ○ Observational cohort-1[16] ○ Randomized open study-3[17,19,20] Clinicaltrials.gov • Recruiting: #12 [31,33,34,35,37,39,40,42,51,61,64,69] • Active: #13[24,26,32,36,41,44,46,47,52,56,57,59,60] • Complete: #29 [25,27-30,38,43,45,48-50,53-55,58,62,63,65-68,70-79]
KQ 3: What are the **comparative harms** associated with antiviral treatments?	Total number of identified systematic reviews: 5 • Completed SR on DAA-2[4,6, 22] • Completed SR on particular DAA-2[1,5]	Size/scope of review Relevant Studies Identified:4 ○ Randomized open study-3[17,19,20] ○ Prospective cohort1[18] Clinicaltrials.gov • Recruiting: #6[31,33,34,40,61,64] • Active: #6[26,32,41,46,47,56] • Complete: #6[27,55,65,74,75,76]
KQ 4: How well do improvements in **intermediate outcomes (SVR, histologic changes) predict reduced morbidity and mortality** in patients with HCV infection?	Total number of identified systematic reviews: 3 • Completed SR/MA-3[7-9]	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov • Recruiting: #0 • Active: #0 • Complete: #0
KQ 5: Are there clinically significant differences in intermediate and health outcomes of antiviral treatment **managed by primary care providers versus subspecialists**?	Total number of identified systematic reviews: 3 • Completed narrative review-2[10-11] • In-process mixed methods review-1[12]	Size/scope of review Relevant Studies Identified: 1 ○ Non-random, open label CT 1[21] Clinicaltrials.gov • Recruiting: #0 • Active: #0 • Complete: #0

Abbreviations: DAA=direct acting antiviral; HCV=hepatitis C virus; MA=meta-analysis; SR=systematic review

Value

This review would be potentially useful to multiple stakeholder groups

- The rise in Hepatitis C infection is tied to the opioid crisis, which is a priority of the HHS Secretary.
- In addition the National Viral Hepatitis Action Plan 2017-2020 (https://www.hhs.gov/hepatitis/action-plan/u-s-viral-hepatitis-action-plan-overview/index.html) outlines the goals, strategies and indicators to track the progress by Federal Agencies to address Hepatitis A, B, and C. A new AHRQ review would be valued by this coalition of Federal colleagues, and can contribute to the goals of the Action Plan.

- The USPSTF is in the process of updating their screening recommendation for Hepatitis C. The draft research plan was posted for public comment September 21, 2017 through October 18, 2017.

Summary of Findings

- Appropriateness and importance: This topic is both appropriate and important, representing a significant disease burden for a large part of the population.
- Duplication: A new review on this topic would not be duplicative of an existing product. Two new direct-acting antiviral regimens have been recently approved by the FDA and are not involved in existing reviews, and few existing reviews have systematically reviewed the evidence on clinical outcomes.
- Impact: Most guidance from Federal sources and others refer to the AASLD/IDSA guidelines on Hepatitis C treatment which was released in April 2017. With the proliferation of new drug regimens, an updated review looking across treatment options is needed.
- Feasibility: A new review may be feasible but the scope would be small. There are a few studies comparing one direct-acting antiviral (DAA) combination regimen to another. Most studies compare the same DAA regimen with immediate vs. deferred timing of therapy, the same 2-3 drug base regimen with or without the addition of ribavirin, or the regimen may include previous or current interferon. Most studies were short-term and looked at sustained viral response for 12 or more weeks (SVR12) and few looked at clinical outcomes. There are many studies in the pipeline, so it is anticipated that additional studies directly comparing DAA regimens may become available in the future.
- Value: This review would be potentially useful to multiple stakeholder groups
    - The rise in Hepatitis C infection is tied to the opioid crisis, which is a priority of the HHS Secretary.
    - A new review could complement the National Viral Hepatitis Action Plan 2017-2020 (https://www.hhs.gov/hepatitis/action-plan/u-s-viral-hepatitis-action-plan-overview/index.html) for Federal Agencies; and an upcoming USPSTF recommendation for Hepatitis C screening.

References

1. Ahmed H, Abushouk AI, Menshawy A, Mohamed A, Negida A, et al. Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with or without Ribavirin for Treatment of Hepatitis C Virus Genotype 1: A Systematic Review and Meta-analysis. Clin Drug Investig. 2017 Sep 4;PubMed PMID: 28871475.

2. Naylor PH, Mutchnick M. Decreasing racial disparity with the combination of ledipasvir-sofosbuvir for the treatment of chronic hepatitis C. Hepat Med. 2017;9:13-16. PubMed PMID: 28356778; PubMed Central PMCID: PMC5360405.

3. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, et al. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. Ann Intern Med. 2017 May 2;166(9):637-648. PubMed PMID: 28319996; NIHMSID: NIHMS862927; PubMed Central PMCID: PMC5486987.

4. Ferreira VL, Tonin FS, Assis Jarek NA, Ramires Y, Pontarolo R. Efficacy of Interferon-Free Therapies for Chronic Hepatitis C: A Systematic Review of All Randomized Clinical Trials. Clin Drug Investig. 2017 Jul;37(7):635-646. PubMed PMID: 28409482

5. Caldeira D, Rodrigues FB, Duarte MM, Sterrantino C, Barra M, et al. Cardiac Harms of Sofosbuvir: Systematic Review and Meta-Analysis. Drug Saf. 2017 Aug 7;PubMed PMID: 28786035.

6. Patel P, Malik K, Krishnamurthy K. Cutaneous Adverse Events in Chronic Hepatitis C Patients Treated With New Direct-Acting Antivirals: A Systematic Review and Meta-Analysis. J Cutan Med Surg. 2016 Jan;20(1):58-66. PubMed PMID: 26162860

7. Bang CS, Song IH. Impact of antiviral therapy on hepatocellular carcinoma and mortality in patients with chronic hepatitis C: systematic review and meta-analysis. BMC Gastroenterol. 2017 Apr 4;17(1):46. PubMed PMID: 28376711; PubMed Central PMCID: PMC5379714.

8. Simmons B, Saleem J, Hill A, Riley RD, Cooke GS. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis. 2016 Mar 15;62(6):683-694. PubMed PMID: 26787172; PubMed Central PMCID: PMC4772843.

9. Wen Y, Zheng YX, Tan de M. A comprehensive long-term prognosis of chronic hepatitis C patients with antiviral therapy: a meta-analysis of studies from 2008 to 2014. Hepat Mon. 2015 May;15(5):e27181. PubMed PMID: 26045707; PubMed Central PMCID: PMC4451277.

10. Wade AJ, Veronese V, Hellard ME, Doyle JS. A systematic review of community based hepatitis C treatment. BMC Infect Dis. 2016 May 16;16:202. PubMed PMID: 27184661; PubMed Central PMCID: PMC4867528

11. Brew IF, Butt C, Wright N. Can antiviral treatment for hepatitis C be safely and effectively delivered in primary care?: a narrative systematic review of the evidence base. Br J Gen Pract. 2013 Dec;63(617):e842-51. PubMed PMID: 24351500; PubMed Central PMCID: PMC3839393.

12. Pourmazi et al (in-process). This in-process mixed methods systematic review will assess the literature on models of care for HCV management to facilitate its management in the primary care setting rather than the tertiary care setting. Outcomes include effectiveness, cost-effectiveness, and acceptability. Author reports it may publish by March 2018.

13. PCORI (in process) Patient-Reported Outcomes Project of HCV-Target (PROPup TARGET). This patient-centered prospective observational cohort of genotype 1 HCV patients will assess harms, benefits of treatment 3 months after it ands, and longer-term toxicities and side effects that occur up to 1 year after treatment end. Project end date September 2019. https://www.pcori.org/research-results/2015/patient-reported-outcomes-project-hcv-target-prop-target

14. PCORI (in process).Comparing Oral Medicines to Treat Hepatitis C Virus (PRIORITIZE). This study is enrolling patients from 45 medical centers with hepatitis C genotype 1 to compare how well two combinations of oral medicines work to cure HCV infection and help patients avoid side effects. This study will look at subpopulations. Project end date August 2021. https://www.pcori.org/research-results/2015/comparing-oral-medicines-treat-hepatitis-c-virus-hcv
15. Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, et al. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology. 2016 Sep;151(3):457-471.e5. PubMed PMID: 27267053; NIHMSID: VAPA850555; PubMed Central PMCID: PMC5341745.
16. Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. Real-world effectiveness of ledipasvir/sofosbuvir in 4,365 treatment-naive, genotype 1 hepatitis C-infected patients. Hepatology. 2016 Aug;64(2):405-14. PubMed PMID: 27115523.
17. Everson GT, Towner WJ, Davis MN, Wyles DL, Nahass RG, et al. Sofosbuvir With Velpatasvir in Treatment-Naive Noncirrhotic Patients With Genotype 1 to 6 Hepatitis C Virus Infection: A Randomized Trial. Ann Intern Med. 2015 Dec 1;163(11):818-26. PubMed PMID: 26551051.
18. Shiffman ML, James AM, Long AG, Alexander PC. Treatment of chronic HCV with sofosbuvir and simeprevir in patients with cirrhosis and contraindications to interferon and/or ribavirin. Am J Gastroenterol. 2015 Aug;110(8):1179-85. PubMed PMID: 26215530.
19. Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. Lancet Infect Dis. 2015 Jun;15(6):645-53. PubMed PMID: 25863559.
20. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014 Nov 15;384(9956):1756-65. PubMed PMID: 25078309.
21. Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, et al. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. Ann Intern Med. 2017 Sep 5;167(5):311-318. PubMed PMID: 28785771.
22. Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017 Sep 18;9:CD012143. PubMed PMID: 28922704.
23. AbbVie. Quality of Life Measurement in Treatment Naïve Patients With HCV Genotype 1 Suffering From Fatigue and Receiving Ombitasvir, Paritaprevir, and Ritonavir and Dasabuvir (HEMATITE). ClinicalTrials.gov. 2017;NCT03002818.
24. AbbVie. The Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in France (OPALE). ClinicalTrials.gov. 2017; NCT02618928.
25. AbbVie. Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C - An Observational Study in Austria (REAL). ClinicalTrials.gov. 2017;NCT 02582658.
26. Kirby Institute. A Phase IV Trial of Paritaprevir/Ritonavir, Ombitasvir, Dasabuvir for Chronic Hepatitis C Genotype 1 Virus Infection (D3FEAT). ClinicalTrials.gov. 2017; NCT02498015.
27. AbbVie. A Study to Evaluate the Efficacy and Safety of Three Experimental Drugs in Adults With Hepatitis C Virus Infection, Who Are Either Treatment-naive or Treatment-experienced in Brazil. ClinicalTrials.gov. 2017;NCT02442271.
28. Gilead Sciences. Ledipasvir/Sofosbuvir Fixed-Dose Combination on Cerebral Metabolism and Neurocognition in Treatment-Naive and Treatment-Experienced Participants With Chronic Genotype 1 HCV Infection. ClinicalTrials.gov. 2016;NCT02219685.

29. Janssen Infectious Diseases BVBA. Efficacy and Safety Study of Simeprevir in Combination With Sofosbuvir in Participants With Chronic Hepatitis C Virus Infection Without Cirrhosis. ClinicalTrials.gov. 2016; NCT02114177.

30. Janssen Infectious Diseases BVBA. Efficacy and Safety Study of Simeprevir in Combination With Sofosbuvir in Participants With Genotype 1 Chronic Hepatitis C Virus Infection and Cirrhosis. ClinicalTrials.gov. 2016;NCT02114151.

31. Istituto Superiore di Sanità. Observational Study in HCV Chronic Infection. ClinicalTrials.gov. 2015;NCT01945008.

32. Gilead Sciences. Efficacy and Safety of Sofosbuvir/Velpatasvir ± Ribavirin for 12 Weeks in Adults With Chronic HCV Infection and Decompensated Cirrhosis. ClinicalTrials.gov. 2017;NCT02996682.

33. Gilead Sciences. Study to Evaluate the Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed-Dose Combination and Ribavarin (CPTC). ClinicalTrials.gov. 2017;NCT02994056.

34. Gilead Sciences. Harvoni in Patients With Chronic Hepatitis C Virus (HCV) Infection in Korea. ClinicalTrials.gov. 2017;NCT02951364.

35. Duke University. Hepatitis C Virus(HCV) Heart and Lung Study. ClinicalTrials.gov. 2017;NCT02858180.

36. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C in Colombia (outCome). ClinicalTrials.gov. 2017;NCT02851069.

37. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin and Patient Support Program in Patients With Chronic Hepatitis C (CITRINE). ClinicalTrials.gov. 2017;NCT02803138.

38. AbbVie. Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C - An Observational Study. ClinicalTrials.gov. 2017;NCT02798315.

39. University of Florida. Study of Oral Treatments for Hepatitis C (PRIORITIZE). ClinicalTrials.gov. 2017;NCT02786537.

40. Gilead Sciences. Sovaldi-based Regimens in Patients in Mexico With Chronic Hepatitis C Virus Infection in Clinical Practice. ClinicalTrials.gov. 2017;NCT02783976.

41. Gilead Sciences. Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination (FDC) and Sofosbuvir/Velpatasvir FDC and Ribavirin in Participants With Chronic Genotype 3 HCV Infection and Cirrhosis. ClinicalTrials.gov. 2017;NCT02781558.

42. University of Nebraska. Determine the Efficacy and Safety of Harvoni in Genotype 1 Chronic Hepatitis c Infected People Who Are Alcoholics. ClinicalTrials.gov. 2017;NCT02759861.

43. Gilead Sciences. Ledipasvir/Sofosbuvir Fixed-Dose Combination for 12 Weeks in Participants With Chronic Genotype 2 HCV Infection. ClinicalTrials.gov. 2017;NCT02738333.

44. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Participants With Chronic Hepatitis C. ClinicalTrials.gov. 2017;NCT02725866.

45. Gilead Sciences. Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Participants With Chronic Hepatitis C Virus Infection. ClinicalTrials.gov. 2017;NCT02722837.

46. Tehran University of Medical Sciences. Sofosbuvir, Ledipasvir, Ribavirin for Hepatitis C Cirrhotics, Genotype 1 (SL50). ClinicalTrials.gov. 2017;NCT02705534.

47. Gilead Sciences. Efficacy and Safety of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Participants With Chronic HCV. ClinicalTrials.gov. 2017;NCT02671500.

48. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C in the Russian Federation - An Observational, Multi-Center Study (HCV RWE). ClinicalTrials.gov. 2017;NCT02669940.

49. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C. ClinicalTrials.gov. 2017;NCT02640547.

50. Gilead Sciences. Safety and Efficacy of SOF/VEL/VOX FDC for 8 Weeks and SOF/VEL for 12 Weeks in Adults Chronic Genotype 3 HCV Infection and Cirrhosis. ClinicalTrials.gov. 2017;NCT02639338.

51. Wilhelminenspital Vienna. Therapy With Ledipasvir/Sofosbuvir in Patients With Genotype 1 HCV Infection Receiving Opiate Substitution Therapy. ClinicalTrials.gov. 2015;NCT02638233.

52. AbbVie. Real World Evidence of the Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C - An Observational Study in Hungary - VERITAS (VERITAS). ClinicalTrials.gov. 2017;NCT02636608.

53. AbbVie. Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With Low-Dose Ribavirin QD in Subjects With Genotype 1a Chronic Hepatitis C Virus Infection (GEODE II). ClinicalTrials.gov. 2017;NCT02609659.

54. Merck Sharp & Dohme Corp. Elbasvir/Grazoprevir (EBR/GZR) and Sofosbuvir (SOF) With and Without Ribavirin (RBV) in Cirrhotic Subjects With Chronic HCV GT3 Infection. ClinicalTrials.gov. 2017;NCT02601573.

55. Tehran University of Medical Sciences. Sofosbuvir, Daclatasvir, Ribavirin for Hepatitis C Virus (HCV) Cirrhotics (SD100). ClinicalTrials.gov. 2016;NCT02596880.

56. Gilead Sciences. Safety and Efficacy of Sofosbuvir-based Regimens in Clinical Practice for the Treatment of Chronic Hepatitis C Virus Infection in India. 2017. ClinicalTrials.gov. 2017; NCT02592057.

57. AbbVie. The Effectiveness of ABT-450/r - Ombitasvir, + Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C -An Observational Study in Ireland (REACH). ClinicalTrials.gov. 2017;NCT02582671.

58. AbbVie. A Study to Evaluate Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir in Treatment-Naïve Hepatitis C Virus Genotype 1b-Infected Adults (GARNET). ClinicalTrials.gov. 2017;NCT02582632.

59. AbbVie. Effectiveness of Paritaprevir/r - Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients With Chronic Hepatitis C in Canada (AMBER). ClinicalTrials.gov. 2017;NCT02581189.

60. AbbVie. Effectiveness of Paritaprevir/Ritonavir - Ombitasvir, +/- Dasabuvir, +/- Ribavirin in Patients With Chronic Hepatitis C - An Observational Study in Belgium. ClinicalTrials.gov. 2017; NCT02581163.

61. Bejing 302 Hospital. Sofosbuvir Containing Regimens for the Treatment of Chronic HCV GT3 Infected Patients. ClinicalTrials.gov. 2017;NCT02576314.

62. AbbVie. Ombitasvir/ABT-450/Ritonavir and Dasabuvir Therapy With Low Dose Ribavirin (RBV), Full Dose RBV or RBV Add-On in Treatment Naive Genotype 1a Hepatitis C Virus Infected Adults. ClinicalTrials.gov. 2017; NCT02493855.

63. Gilead Sciences. Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination, With or Without Ribavirin, in Egyptian Adults With Chronic Genotype 4 HCV Infection. ClinicalTrials.gov. 2017;NCT02487030.

64. Humanity and Health Research Centre. Sofosbuvir Containing Regimens for the Treatment of Chronic HCV GT2 Infected Patients. ClinicalTrials.gov. 2017;NCT02482077.

65. Stanford University. Comparative Efficacy of Fixed-dose Combination Sofosbuvir + Ledipasvir, 8 vs. 12 Weeks in Chronic Hepatitis C Genotype 6. ClinicalTrials.gov. 2017;NCT02480166.

66. Bejing Hospital 302. Triple DAAs Regimen in Treating Non-cirrhotic HCV GT1b Subjects. ClinicalTrials.gov. 2016;NCT02470858.

67. AbbVie. A Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With or Without Ribavirin in US Veterans With Genotype 1 Chronic Hepatitis C Virus Infection. ClinicalTrials.gov. 2017;NCT02442284.

68. AbbVie. Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir Co-Administered With Sofosbuvir With and Without Ribavirin in Treatment-Naive HCV Genotype 1-Infected Adults. ClinicalTrials.gov. 2016;NCT02399345.

69. Valme University Hospital. Efficacy and Safety of Therapy Against HCV Based on Direct-acting Antivirals in Real-life Conditions (FPSMON201401). ClinicalTrials.gov. 2016;NCT02333292.

70. Gilead Sciences. Comparison of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks With Sofosbuvir and Ribavirin for 12 Weeks in Adults With Chronic Genotype 2 HCV Infection (ASTRAL-2). ClinicalTrials.gov. 2016;NCT02220998.

71. Gilead Sciences. Efficacy and Safety of Oral Regimens for the Treatment of Chronic HCV Infection. ClinicalTrials.gov. 2017;NCT 02202980.

72. Gilead Sciences. Comparison of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks With Sofosbuvir and Ribavirin for 24 Weeks in Adults With Chronic Genotype 3 HCV Infection (ASTRAL-3). ClinicalTrials.gov.2017;NCT02201953.

73. Gilead Sciences. Sofosbuvir/Velpatasvir Fixed-Dose Combination in Adults With Chronic HCV Infection and Child-Pugh Class B Cirrhosis (ASTRAL-4). ClinicalTrials.gov. 2016;NCT02201901.

74. Bristol-Myers Squibb. UNITY 2: A Study of an Investigational Treatment Regimen of DCV+ASV+BMS-791325 in a Fixed Dose Combination (the DCV 3DAA (Direct Acting Antiviral) Regimen) With or Without RBV for 12 Weeks for the Treatment of Chronic Hepatitis C Virus(HCV)Genotype 1 Infection in Subjects With Compensated Cirrhosis. ClinicalTrials.gov. 2015;NCT01973049.

75. Merck Sharp & Dohme Corp. Efficacy and Safety of Combination Grazoprevir (MK-5172) + Elbasvir (MK-8742) + Ribavirin (RBV) in Genotype 2 Hepatitis C Infection (MK-5172-047). ClinicalTrials.gov. 2017;NCT01932762.

76. Gilead Sciences. Safety and Efficacy of Sofosbuvir + Velpatasvir With or Without Ribavirin in Treatment-Naive Adults With Chronic HCV Infection. ClinicalTrials.gov. 2016;NCT01858766.

77. Gilead Sciences. Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination ± Ribavirin for the Treatment of HCV (ION-3). ClinicalTrials.gov. 2014;NCT01851330.

78. National Institute of Allergy and Infectious Disease. Combination Therapy for Chronic Hepatitis C Infection. ClinicalTrials.gov. 2017;NCT01805882.

79. Gilead Sciences. Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed-Dose Combination (FDC) With and Without Ribavirin for the Treatment of HCV. ClinicalTrials.gov. 2015;NCT01701401.

Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, DAA for HCV treatment are available in the US.
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	The CDC found that new hepatitis C infections nearly tripled between 2010 and 2015, and estimates that there were about 34,000 new hepatitis C infections in 2015 (https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm). Approximately 75%–85% of people who become infected with Hepatitis C virus develop chronic infection. An estimated 2.7-3.9 million people in the United States have chronic hepatitis C (https://www.cdc.gov/hepatitis/hcv/cfaq.htm).
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	According to the CDC, increases in acute HCV case reports reflect new infections associated with rising rates of injection-drug use, and, to a much lesser extent, improved case detection. Several early investigations of newly acquired HCV infections reveal that most occur among young, white persons who live in non-urban areas (particularly in states within the Appalachian, Midwestern, and New England regions of the country; trends in these states likely indicate an overall increase in HCV incidence throughout the country
2c. Represents important uncertainty for decision makers	Yes, there various treatment regimens and information is needed about comparative effectiveness. HCV treatment improved drastically in 2011 with development of the initial direct-acting oral agents. Two new drugs were FDA-approved in the past few months, glecaprevir/pibrentasvir (Mavyret) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi). With the proliferation of new drug regimens an updated review looking across treatment options is needed. HCV genotype 1 represent 60% to 75% of HCV infections in the United States, and is more difficult to cure than genotype 2 or genotype 3.

	In addition there is interest in having primary care clinicians provide DAA therapy, and there is uncertainty about how outcomes would compare to treatment provided by a specialty clinician.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, treatment is expensive. CMS estimated that total drug spending in 2014 was up 11.3 percent for private health insurance, 16.9 percent in Medicare, and 24.3 percent in Medicaid, citing hepatitis C drugs as a factor in each sector. Spending on hepatitis C drugs also contributed to the rise in Medicare Part D spending per beneficiary, which increased by only about 2 percent in 2013, but by more than 8 percent in both 2014 and 2015, according to the 2016 Medicare trustees report. Preliminary estimates, based on data obtained from CMS by the Associated Press, suggest that 2015 spending on the new hepatitis C drugs was $9.2 billion or roughly double the 2014 levels. (http://healthaffairs.org/blog/2016/11/03/the-cost-of-a-cure-revisiting-medicare-part-d-and-hepatitis-c-drugs/)
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new review would not be duplicative. Available reviews cover portions of the scope, and few reviews have systematically reviewed the evidence on clinical outcomes. In addition two new DAA regimens have been recently approved by the FDA and are not included in existing reviews. KQ 1 (clinical outcomes). • Jakobsen et al (2017). Clinical outcomes included mortality, morbidity, hr QoL KQ 2 (intermediate outcomes). • Jakobsen et al (2017). Examined DAA on SVR. • Falade-Nwulia et al (2017). This SR examined oral DAA on SVR in patients, but included populations explicitly excluded in the PICOTS (HIV infection, renal failure, liver transplantation, and treatment-experienced people). • Ferreira et al (2017). This SR reviewed DAA on SVR and relapse in both treatment-experienced and treatment-naïve individuals. Results for treatment-naïve individuals were not presented separately. • Ahmed et al (2014). This SR reviewed the literature on Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir on individuals with genotype 1.

	• Naylor et al (2017). This review examined differences in achievement of SVR after ledipasvir/sofosbuvir treatment between Caucasians and African-Americans. KQ 3 (harms of treatment) • Jakobsen et al (2017). Examined adverse effects of DAA • Caldeira et al (2017). This review focused specifically on cardiac harms of sofosbuvir. • Patel et al (2016). This SR focused on cutaneous adverse events related to DAA. • Falade-Nwulia et al (2017) • Ahmed et al (2014) KQ 4 (Association of SVR with clinical outcomes). • Bang et al (2017). This SR/MA examined the development of HCC and mortality in patients who achieved SVR compared to those who did not. • Simmons et al (2016). This SR/MA examined the risk of late relapse or reinfection with HCV after SVR in low-risk, high-risk and HIV/HCV co-infected populations. In most studies, individuals were treated with IFN-based therapies. • Wen et al (2014). This SR examined the risk of all-cause mortality and HCC in individuals who had achieved SVR compared to those who did not. KQ 5 (Primary vs. Specialty care). • Wade et al (2016) was a narrative review looked at studies comparing primary vs. tertiary based services for hepatitis C treatment. Outcomes included treatment uptake and SVR outcomes. • Brew et al (2013). This narrative review examined studies on the provision of community-based antiviral treatment compared to hospital outpatient settings. The studies included were those of individuals on interferon/ribavirin treatment. • Pourmazi et al (in-process). This in-process mixed methods systematic review will assess the literature on models of care for HCV management to facilitate its management in the primary care setting rather than the tertiary care setting. Outcomes include effectiveness, cost-effectiveness, and acceptability.
4. Impact of a New Evidence Review	

4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Most guidance from Federal sources and others refer to the AASLD/IDSA guidelines on Hepatitis C treatment, which was released in April 2017. However, two new drugs were FDA-approved in the past few months, glecaprevir/pibrentasvir (Mavyret) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi). With the proliferation of new drug regimens an updated review looking across treatment options is needed.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Unknown, but likely there is variation due to the many available treatment options and newly available drugs.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new AHRQ review is feasible. There are a few studies comparing one direct-acting antiviral (DAA) combination regimen to another. Most studies compare the same DAA regimen with immediate vs. deferred timing of therapy, the same 2-3 drug base regimen with or without the addition of ribavirin, or the regimen may include previous or current interferon. Most studies were short-term and looked at sustained viral response for 12 or more weeks (SVR12). Only a few studies looked at clinical outcomes. There are many studies in the pipeline, so it is anticipated that additional studies directly comparing DAA regimens may become available in the future. • If the scope focused only on head-to-head comparisons of DAAs (as described in this brief) the scope would be small. • If the scope were broadened to include comparators other than DAAs, the estimated scope would be large.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	The rise of HCV infection has been tied to the opioid crisis, which is a priority by the HHS Secretary. In addition the National Viral Hepatitis Action Plan 2017-2020 (https://www.hhs.gov/hepatitis/action-plan/u-s-viral-hepatitis-action-plan-overview/index.html) outlines the goals, strategies and indicators to track the progress by Federal Agencies to address Hepatitis A, B, and C. A new AHRQ review would be valued by this coalition of Federal colleagues, and can contribute to the goals of the Action Plan. The USPSTF is in the process of updating their screening recommendation for Hepatitis C. The draft research plan was posted for public comment September 21, 2017 through October 18, 2017.

6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	American Academy of Family Physicians (AAFP) will use the SR to inform a clinical practice guideline.

Appendix B. Search Strategy Results (Feasibility)

Topic: Hepatitis C Treatment Date: September 27, 2017 Database Searched: PubMed	
Concept	**Search String**
Hepatitis C Treatment in Treatment Naive	(((((((("hepatitis c"[MeSH Terms] OR "hepatitis c"[All Fields] OR "hepacivirus"[MeSH Terms] OR "hepacivirus"[All Fields]) AND treatment[Title]) OR therapy[Title]) AND "antiviral"[All Fields]) AND “treatment naïve” [Text Word]
Not Editorials, etc.	NOT "letter"[Publication Type]) NOT "news"[Publication Type]) NOT "patient education handout"[Publication Type]) NOT "comment"[Publication Type]) NOT "editorial"[Publication Type]) NOT "newspaper article"[Publication Type]
Limit to Adults, last 5 years, Human, English	Filters activated: published in the last 5 years, Humans, English, Adult: 19 years and up.
N=218	

Clinicaltrials.gov

70 Studies found for:

antiviral treatment | Recruiting Studies | hepatitis C | Antiviral Agents | First posted from 12/01/2011 to 12/31/2016

https://clinicaltrials.gov/ct2/results?term=antiviral+treatment&type=&rslt=&recrs=a&age_v=&gndr=&cond=hepatitis+C&intr=Antiviral+Agents&titles=&outc=&spons=&lead=&id=&cntry1=&state1=&cntry2=&state2=&cntry3=&state3=&locn=&sfpd_s=12%2F1%2F2011&sfpd_e=12%2F31%2F2016&lupd_s=&lupd_e=

49 Studies found for:

antiviral treatment | Active, not recruiting Studies | hepatitis C | First posted from 12/01/2011 to 12/31/2016

ttps://clinicaltrials.gov/ct2/results?term=antiviral+treatment&type=&rslt=&recrs=d&age_v=&gndr=&cond=hepatitis+C&intr=&titles=&outc=&spons=&lead=&id=&cntry1=&state1=&cntry2=&state2=&cntry3=&state3=&locn=&sfpd_s=12%2F1%2F2011&sfpd_e=12%2F31%2F2016&lupd_s=&lupd_e=

302 Studies found for:

antiviral treatment | Completed Studies | hepatitis C | First posted from 12/01/2011 to 12/31/2016

https://clinicaltrials.gov/ct2/results?term=antiviral+treatment&type=&rslt=&recrs=e&age_v=&gndr=&cond=hepatitis+C&intr=&titles=&outc=&spons=&lead=&id=&cntry1=&state1=&cntry2=&state2=&cntry3=&state3=&locn=&sfpd_s=12%2F1%2F2011&sfpd_e=12%2F31%2F2016&lupd_s=&lupd_e=