2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration effects

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Other

SRC Literature Analysis:

- One study found that a higher percentage of patients who received immunotherapy with TG4040 followed by TG4040 and PEG-IFNα/RBV achieved a cEVR compared with patients who received only PEG-IFNα/RBV therapy

Reviewer Questions:

3. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

4. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 2b:

How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 3:

Do these harms differ according to patient subgroup characteristics?
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Key Question 4:

Have improvements in intermediate outcomes been shown to reduce risk or rates of adverse health outcomes from HCV infection?

Mortality and long-term hepatic complications

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Short-term quality of life

SRC Literature Analysis:

- No new research was found

Reviewer Questions:

1. Are the original report conclusions still supported by the current evidence?

Click here to enter text.

2. Are there any published or unpublished studies that you know of that we may have overlooked?

Click here to enter text.

Title of Original Review: TBD

Link to Report

The conclusions from the original report and an analysis of recent literature identified by the Scientific Resource Center (SRC) are summarized below. Abstracts are provided for included literature at the end of the document.

Conclusions From Original Review, SOE = Strength of Evidence	SRC Literature Analysis
Key Question 1a: What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?	
Long-term clinical outcomes **SOE: Insufficient** No evidence.	No new research was found
Short-term mortality **SOE: Low** 3 trials compared current antiviral regimens[1], but found no difference in short-term mortality. Very few (20 total) events reported.	No new research was found
Short-term quality of life **SOE: Low** Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin (1 open-label randomized trial) found slightly better short-term scores favoring pegylated interferon alfa-2a plus ribavirin for patients with genotype-4 infection.	No new research was found
Key Question 1b: How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	
Any clinical outcome **SOE: Insufficient** No evidence.	No new research was found
Key Question 2a: What is the comparative effectiveness of antiviral treatments on intermediate outcomes?	
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Moderate** 7 trials found pegylated interferon alfa-2b plus ribavirin to be associated with lower likelihood of achieving an SVR (pooled RR 0.87, 95% CI: 0.80 to 0.95; I_2=27.4%)	No new research was found

• Absolute difference in SVR rates: 8% (95% CI: 3 to 14)	
Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Duration Effects **Outcome: Sustained viroligic response** **SOE: Moderate** 48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin: • 2 trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving SVR (pooled RR 0.97, 95% CI: 0.84 to 1.1; I_2=43%) 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b): • 4 trials of patients with genotype 2 or 3 infection favored 24 weeks of therapy more effective for achieving SVR (pooled RR 1.15; 95% CI: 1.02 to 1.29; I_2=79.5%) • Relative risk estimates: 1.01 to 1.33; may vary due to differences across studies in ribavirin dosing. 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin: • 3 trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences (RR 0.99, 95% CI: 0.86 to 1.14; I_2=66.7%). • Relative risk estimates: 0.89 to 1.2.	No new research was found
Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects **Outcome: Sustained viroligic response** **SOE: Moderate** Low (0.75-1.0 mcg/kg or 50 mcg) vs. high doses (1.5 mcg/kg or 100-150 mcg) of pegylated interferon alfa-2b : • 6 trials found lower doses associated with lower likelihood of achieving SVR for patients with genotype 2 or 3 infection (Pooled RR 0.90; 95% CI: 0.81 to 0.99; I_2=20.2%) Low (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. high doses (800 or 1,200 mg flat dose or 800 to 1,400 mg weight-based dose) of ribavirin: • 3 trials of patients with genotype 2 or 3 infection who did not specifically have	No new research was found

advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR. **SOE: Low** 48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1,000 mg daily) vs. 48 weeks of triple therapy with a standard ribavirin dose (800-1,400 mg daily): • 1 trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin to be associated with a non–statistically significant trend toward lower likelihood of SVR (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3)	
Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Moderate** Triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 3 trials of patients with genotype 1 infection found triple therapy with telaprevir to be associated with a higher likelihood of SVR (pooled RR 1.48, 95% CI: 1.26 to 1.75; I_2=0.0%) • Absolute increase in SVR rate: 22% (95% CI 13 to 31). Triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. . dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 1 trial of patients with genotype 1 infection found no difference in likelihood of SVR **SOE: Low** Response guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by a response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 1 trial of patients with genotype 1 infection found response guided triple therapy with telaprevir to be associated with higher likelihood of SVR. • Absolute increase in SVR rate: 25% to 31%	No new research was found

8 week telaprevir vs. 12 week teleprevir regimen: • 8 week regimen associated with a slightly lower SVR rate (69% vs. 75%) Triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) vs. triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy). • 1 trial of patients with genotype 1 found no difference in likelihood of SVR.	
Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration effects **Outcome: Sustained viroligic response** **SOE: Low** 1 trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1,125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b). 1 trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.	No new research was found
Not in original CER	One RCT examined the new vaccine TG4040 and compared dual therapy with PEG-IFNα/RBV for 48 weeks (Group A) to triple therapy with PEG-IFNα/RBV for 4 weeks followed by PEG-IFNα/RBV for 44 weeks with 6 injections of TG4040 (Group B) to triple therapy with TG4040 for 12 weeks (7 injections) followed by PEG-IFNα/RBV for 48 weeks with 6 injections of TG4040 (Group C). Findings indicated that after 24 weeks, A higher percentage of patients achieved a

	sustained virologic response 24 weeks after therapy ended in group C (58.2%) than in groups A (48.4%) or B (50.8%)
Key Question 2b: How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?	
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Low** Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: • Largest trial (N=3,070) found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. • Characteristics associated with lower absolute SVR rates: o Older age o Black race o Advanced fibrosis or cirrhosis o High baseline viral load **SOE: Moderate** Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: • 4 trials found no clear differences in relative risk estimates for SVR in patients stratified by genotype. • Genotype 1 infection was associated with lower absolute SVR rate than genotypes 2 and 3.	No new research was found
Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Moderate** Triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon,	No new research was found

ribavirin, and boceprevir) (2 trials): • Men vs. Women: No difference in relative risk estimates for SVR • Blacks vs. Non-Black patients: No clear difference in relative risk estimates. Black race associated with lower SVR. Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: • 2 trials found triple therapy to be associated with a higher likelihood of achieving SVR in patients with high baseline HCVRNA viral load (>600,000 or 800,000 IU/mL). Found no difference in likelihood of SVR in patients of lower viral load.	
Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Moderate (for age and sex); Low (for other factors)** Response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks: • 1 trial found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or BMI. • Characteristics associated with lower absolute SVR rates: o Older age o Black race o Advanced fibrosis or cirrhosis o Higher BMI 24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy: • 1 trial found no differences in estimates of effect in patients stratified by sex or age. **SOE: Insufficient** Triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy: 2 trials reported inconsistent findings for differential relative risk estimates according to baseline	No new research was found

viral load.	
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Harms** **SOE: Moderate** Dual therapy with pegylated interferon alfa-2b vs. dual therapy with pegylated interferon alfa-2a plus ribavirin: • Dual therapy with pegylated interferon alfa-2b was associated with: o Slightly greater risk of headache (3 trials), pooled RR 1.1, 95% CI 1.1 to 1.2; I2=0%) o Lower risk of serious adverse events (2 trials), pooled RR 0.76; 95% CI 0.71 to 0.88; I2=0%) o Lower risk of neutropenia (5 trials), pooled RR 0.61, 95% CI 0.46 to 0.83; I2=38% o Lower risk of rash (2 trials), pooled RR 0.79, 95% CI 0.71 to 0.88; I2=0.0%). • Found no difference in withdrawals due to adverse events.	No new research was found
Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Moderate** Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: • Triple therapy with boceprevir was associated with: o Increased risk of neutropenia (2 trials), pooled RR 1.8, 95% CI 1.5 to 2.3; I2=0.0% o Dysgeusia (2 trials), pooled RR 2.5, 95% CI 2.0 to 3.2; I2=0.0% o Anemia (2 trials), pooled RR 2.0, 95% CI 1.4 to 2.8; I2=0.0% o Thrombocytopenia (2 trials), pooled RR 3.2, 95% CI 1.2 to 8.2; I2=0.0% • % Incidence in triple therapy: o Anemia: 25% o Neutropenia: 33% o Severe anemia: 4-5% o Severe neutropenia: 8-15%	No new research was found

Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Moderate** 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin: • 2 trials found no statistically significant difference in risk of any assessed adverse event. 24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 3 trials found triple therapy to be associated with: o Increased risk of anemia (3 trials), pooled RR 1.3, 95% CI 1.1 to 1.5; I2=0.0% o Rash (3 trials), pooled RR 1.4, 95% CI 1.1 to 1.7, I2=0.0% • Patients randomized to the telaprevir therapy experienced: o Rash (1 to 2/3 of entire group) o Anemia: 27-91% o Severe rash: 7-10% o Severe anemia: 4-11% • No difference in risk of withdrawal due to adverse events. **SOE: Low** Response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 1 trial found association between triple therapy and: o Increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7) o Anemia(38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5) o Any rash (36% vs. 24%, RR 1.5, 95% CI 1.2 to 1.8) o Severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13)	No new research was found
Key Question 3: Do these harms differ according to patient subgroup characteristics?	

Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Harms** **SOE: Insufficient** Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin: • No trials reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. • 3 trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	No new research was found
Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Insufficient** Triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin: • No trial evaluated harms in patient sugbroups. • All trials evaluated patients with genotype 1 infection	
Key Question 4: Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?	
Outcome: Mortality and long-term hepatic complications **SOE: Moderate** SVR after antiviral therapy vs. no SVR: • 1 large VA hospital study found SVR after antiviral therapy to be associated with lower risk of all-cause mortality (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). • 18 cohort studies found SVR to be associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD • Studies had methodological shortcomings, including inadequate handling of confounders. 10 were conducted in Asia.	No new research was found
Outcome: Short-term quality of life **SOE: Low**	No new research was found

SVR vs. no SVR: • 9 studies found SVR to be associated with greater improvement in measures related to QoL (generic or disease-specific) 24 weeks after the end of antiviral treatment. o Differences averaging 5 to 10 points on various SF-36 domains. • All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to follow-up, and failure to blind patients to SVR status.	

Legend: HCV = hepatitis c virus infection; SVR = sustained viroligic response; RR = relative risk; HCV-RNA = hepatitis c virus-ribonucleic acid; BMI = body mass index; ESLD = end-stage liver disease; QoL = quality of life

[1] "Current antiviral treatment regimen" refers to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin and boceprevir or telaprevir.

Abstract from Relevant Literature

Di Bisceglie et al.2014

Efficacy of immunotherapy with TG4040, peg-interferon, and ribavirin in a Phase 2 study of patients with chronic HCV infection, Gastroenterology

BACKGROUND & AIMS: TG4040 is a modified vaccinia Ankara (MVA) virus that expresses the hepatitis C virus (HCV) proteins NS3, NS4, and NS5B. We performed a phase II open-label study to determine the efficacy, safety, and immunotherapeutic properties of TG4040 in combination with pegylated interferon alpha-2a and ribavirin (PEG-IFNalpha/RBV) in patients with chronic HCV infection.;METHODS: Treatment-naive patients with HCV genotype 1 infection were assigned randomly to 1 of the following groups: PEG-IFNalpha/RBV for 48 weeks (group A, n = 31), PEG-IFNalpha/RBV for 4 weeks followed by PEG-IFNalpha/RBV for 44 weeks with 6 injections of TG4040 (group B, n = 63), or TG4040 for 12 weeks (7 injections) followed by PEG-IFNalpha/RBV for 48 weeks with 6 injections of TG4040 (group C, n = 59). The primary end point was complete early virologic response (cEVR), defined as HCV-RNA level less than 10 IU/mL after 12 weeks of PEG-IFNalpha/RBV treatment.;RESULTS: In group C, 64.2% of evaluable patients achieved cEVR, compared with 30.0% in group A and 45.9% in group B (P = .0003 for group C vs A). A higher percentage of patients achieved a sustained virologic response 24 weeks after therapy ended in group C (58.2%) than in groups A (48.4%) or B (50.8%). HCV- and MVA-specific T-cell responses were observed predominantly in group C. As expected, most patients given injections of TG4040 developed anti-MVA antibodies. The combination of TG4040 and PEG-IFNalpha/RBV was reasonably well tolerated. However, PEG-IFNalpha-associated thrombocytopenia developed in 3 patients who carried the class II HLA allele DRB01*04.;CONCLUSIONS: A higher percentage of patients with chronic HCV infection who received immunotherapy with TG4040 followed by TG4040 and PEG-IFNalpha/RBV achieved a cEVR compared with patients who received only PEG-IFNalpha/RBV therapy. These findings show that immunotherapies that activate T cells are effective in patients with chronic HCV infection. ClinicalTrials.gov number, NCT01055821.

Appendix G. Summary Table

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
Key Question 1a: What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?				
Long-term clinical outcomes **SOE: Insufficient** No evidence.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S. One reviewer recommended five articles. Of these articles, none met inclusion criteria. One articles was a case study[1] examining the duration of surveillance, another was a study examining predictive models of clinical outcomes[2], one examined biomarkers up to 24 weeks[3], another study examined long term outcomes associated with pegylated interferon alpha and ribavirin therapy[4], and the final	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			was a review that that did not compare the effectiveness of long term outcomes.[5]	
Short-term mortality **SOE: Low** 3 trials compared current antiviral regimens[1], but found no difference in short-term mortality. Very few (20 total) events reported.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Short-term quality of life **SOE: Low** Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin (1 open-label randomized trial) found slightly better short-term scores favoring pegylated interferon alfa-2a plus ribavirin for patients with genotype-4 infection.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	Two of the three reviewers agreed that the conclusions in the original CER were current. One reviewer noted that there is markedly new evidence regarding quality of life associated with new direct acting antivirals. Two studies were provided; however, were not comparative effectiveness studies, thus did not meet inclusion criteria.[6,7]	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	
Key Question 1b: How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?				
Any clinical outcome **SOE: Insufficient** No evidence.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. However, two reviewers noted that new HCV medications had not been addressed in the 2015 literature search, and that Telaprevir and Boceprevir are no longer marketed, and that pegylated interferon is not being used in the U.S.	Original conclusion is still valid and this portion of the CER is likely current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Key Question 2a: What is the comparative effectiveness of antiviral treatments on intermediate outcomes?				
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Sustained viroligic response** **SOE: Moderate**	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
7 trials found pegylated interferon alfa-2b plus ribavirin to be associated with lower likelihood of achieving an SVR (pooled RR 0.87, 95% CI: 0.80 to 0.95; I_2=27.4%) • Absolute difference in SVR rates: 8% (95% CI: 3 to 14)			being used in the U.S.	used in the U.S., this conclusion is not applicable to current practice.
Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Duration Effects **Outcome: Sustained viroligic response** **SOE: Moderate** 48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin: • 2 trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving SVR (pooled RR 0.97, 95% CI: 0.84 to 1.1; I_2=43%) 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b): • 4 trials of patients with genotype 2 or 3 infection favored 24 weeks of therapy more effective for achieving SVR (pooled RR 1.15; 95% CI: 1.02 to 1.29; I_2=79.5%) • Relative risk estimates: 1.01 to 1.33; may vary due to differences across studies in ribavirin dosing. 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin: • 3 trials of patients with genotype	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences (RR 0.99, 95% CI: 0.86 to 1.14; I_2=66.7%). • Relative risk estimates: 0.89 to 1.2.				
Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin: Dose Effects **Outcome: Sustained viroligic response** **SOE: Moderate** Low (0.75-1.0 mcg/kg or 50 mcg) vs. high doses (1.5 mcg/kg or 100-150 mcg) of pegylated interferon alfa-2b : • 6 trials found lower doses associated with lower likelihood of achieving SVR for patients with genotype 2 or 3 infection (Pooled RR 0.90; 95% CI: 0.81 to 0.99; I_2=20.2%) Low (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. high doses (800 or 1,200 mg flat dose or 800 to 1,400 mg weight-based dose) of ribavirin: • 3 trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR.	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
○ Lower risk of serious adverse events (2 trials), pooled RR 0.76; 95% CI 0.71 to 0.88; I_2=0%) ○ Lower risk of neutropenia (5 trials), pooled RR 0.61, 95% CI 0.46 to 0.83; I_2=38% ○ Lower risk of rash (2 trials), pooled RR 0.79, 95% CI 0.71 to 0.88; I_2=0.0%). • Found no difference in withdrawals due to adverse events.				
Triple therapy with Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Moderate** Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: • Triple therapy with boceprevir was associated with: ○ Increased risk of neutropenia (2 trials), pooled RR 1.8, 95% CI 1.5 to 2.3; I_2=0.0% ○ Dysgeusia (2 trials),	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.[8]	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
pooled RR 2.5, 95% CI 2.0 to 3.2; I_2=0.0% o Anemia (2 trials), pooled RR 2.0, 95% CI 1.4 to 2.8; I_2=0.0% o Thrombocytopenia (2 trials), pooled RR 3.2, 95% CI 1.2 to 8.2; I_2=0.0% • % Incidence in triple therapy: o Anemia: 25% o Neutropenia: 33% o Severe anemia: 4-5% o Severe neutropenia: 8-15%				
Triple therapy with Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Moderate** 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin: • 2 trials found no statistically significant difference in risk of any assessed adverse event. 24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.[8]	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
alfa-2a plus ribavirin for 12 weeks) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 3 trials found triple therapy to be associated with: o Increased risk of anemia (3 trials), pooled RR 1.3, 95% CI 1.1 to 1.5; I_2=0.0% o Rash (3 trials), pooled RR 1.4, 95% CI 1.1 to 1.7, I_2=0.0% • Patients randomized to the telaprevir therapy experienced: o Rash (1 to 2/3 of entire group) o Anemia: 27-91% o Severe rash: 7-10% o Severe anemia: 4-11% • No difference in risk of withdrawal due to adverse events. **SOE: Low** Response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks: • 1 trial found association between triple therapy and: o Increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI				

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
2.6 to 5.7) o Anemia(38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5) o Any rash (36% vs. 24%, RR 1.5, 95% CI 1.2 to 1.8) o Severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13)				
Key Question 3. Do these harms differ according to patient subgroup characteristics?				
Dual therapy with Pegylated Interferon Alfa-2b plus Ribavirin vs. Dual therapy with Pegylated Interferon Alfa-2a plus Ribavirin **Outcome: Harms** **SOE: Insufficient** Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin: • No trials reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. • 3 trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	No new research was identified.	None identified	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One[9] reviewer provided a study comparing PEG-IFN alfa-2a (180 µg/week; n=402) to PEG-IFN alfa-2b (1.5 µg/kg/week; n=259) with ribavirin (800–1200 mg/day) for 24 or 48 weeks in Korea, and found that unlike the Western data, efficacy and safety of PEG-IFN alfa-2a were similar to those of PEG-IFN alfa-2b in chronically HCV-infected Korean patients regardless of	Original conclusion is still valid and this portion of the CER is likely still current; however, due to pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
			age, HCV viral load, and hepatic fibrosis.	
Triple therapy with Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir or Boceprevir vs. Dual therapy with Pegylated Interferon Alfa-2a or Alfa-2b plus Ribavirin **Outcome: Harms** **SOE: Insufficient** Triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin: • No trial evaluated harms in patient sugbroups. • All trials evaluated patients with genotype 1 infection.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	All three reviewers agreed that the conclusions in the original CER were current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One reviewer provided a study examining triple therapy; however, this was not a comparative effectiveness study.[8]	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Key Question 4. Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?				
Outcome: Mortality and long-term hepatic complications **SOE: Moderate** SVR after antiviral therapy vs. no SVR: • 1 large VA hospital study found SVR after antiviral therapy to be associated with lower risk of all-cause mortality (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	Two reviewers agreed that the conclusions in the original CER were current. One reviewer noted that the conclusions were partially current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S.	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment
0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). • 18 cohort studies found SVR to be associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD • Studies had methodological shortcomings, including inadequate handling of confounders. 10 were conducted in Asia.				pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.
Outcome: Short-term quality of life **SOE: Low** SVR vs. no SVR: • 9 studies found SVR to be associated with greater improvement in measures related to QoL (generic or disease-specific) 24 weeks after the end of antiviral treatment. o Differences averaging 5 to 10 points on various SF-36 domains. • All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to follow-up, and failure to blind patients to SVR status.	No new research was identified.	Telaprevir Incivek (Discontinued - after 3/25/2014): "WARNING: Serious Skin Reactions…including Stevens Johnson Syndrome..."	Two reviewers agreed that the conclusions in the original CER were current. One reviewer noted that the conclusions were partially current. Two reviewers noted that the conclusions are irrelevant due to pegylated interferon no longer being used in the U.S. One reviewer noted that there is markedly new evidence regarding quality of life associated with new direct acting antivirals. Two studies were provided; however, were not comparative effectiveness studies, thus did not meet inclusion criteria.[6,7]	Original conclusion is still valid, and this portion of the CER is likely still current; however, due to Telaprevir and Boceprevir no longer being marketed, and pegylated interferon no longer being used in the U.S., this conclusion is not applicable to current practice.

Conclusions From CER Executive Summary	Literature Analysis (July 2015)	FDA Boxed Warnings	Expert Opinion	Surveillance Assessment

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