

## **Treatment of Hepatitis C Virus Infection in Adults: Future Research Needs**

**Identification of Future Research Needs From Comparative Effectiveness Review  
No. 76**

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The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

We welcome comments on this Future Research Needs document. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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# Executive Summary

## Background

In 2010 the Agency for Healthcare Research and Quality (AHRQ) charged the Oregon Evidence-based Practice Center (EPC) with conducting a Comparative Effectiveness Review (CER)<sup>1</sup> on antiviral treatments for hepatitis C virus (HCV) infection. The CER focused on current, U.S. Food and Drug Administration (FDA)-approved antiviral therapies for antiviral-naïve adults with chronic HCV infection, without HIV or hepatitis B virus coinfection.

The Key Questions addressed in the CER were:

### Key Question 1:

1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?

1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

### Key Question 2:

2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of sustained virologic response (SVR) or histologic changes in the liver?

2b. 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:

3a. What are the comparative harms associated with antiviral treatments?

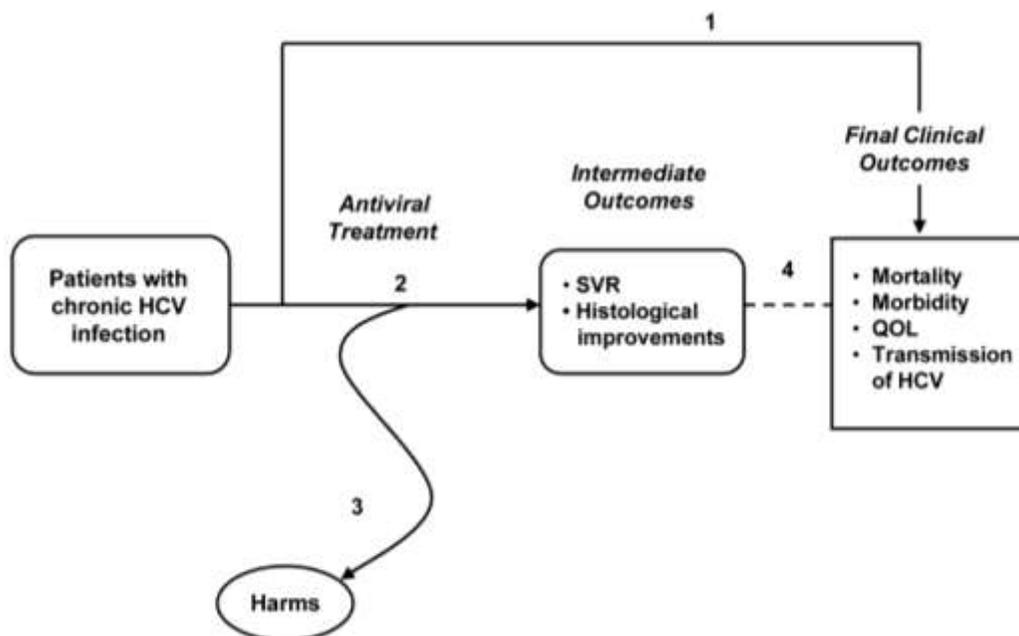
3b. Do these harms differ according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

### Key Question 4:

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

The analytic framework (Figure A) illustrates the targeted population, interventions, and outcomes for the CER.

**Figure A. Analytic framework from Comparative Effectiveness Review**



Note: HCV=hepatitis C virus, QOL=quality of life, SVR=sustained virologic response.

The CER's objectives were to understand the comparative benefits and harms of the various antiviral regimens to make informed treatment decisions in antiviral-naïve patients with chronic HCV infection, particularly given the availability of new treatment options. The review evaluated the effects of different medication doses, durations of therapy, and dosing strategies, and examined how comparative effectiveness varies depending on HCV genotype, viral load, and other demographic and clinical characteristics. The CER did not evaluate antiviral treatment of HCV-infected patients with HIV or hepatitis B coinfection, pregnant women, or children.

Research gaps and limitations of the existing literature identified in the CER are summarized below, organized according to the most relevant element of the population, intervention, comparator, outcome, and timing (PICOT) framework:

**Population-Related Gaps:**

1. Need for studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice (relevant to all Key Questions).
2. Need for studies of treatment in screen-detected patients, to understand applicability to this population (relevant to all Key Questions).
3. Need for studies designed using an effectiveness paradigm, to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than observed in efficacy trials (relevant to all Key Questions).
4. Need for studies on effects of newer triple therapy regimens with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors (relevant to Key Questions 2b, 3b).

**Intervention-Related Gaps:**

5. Need for head-to-head studies comparing triple therapy with newer protease inhibitors (telaprevir and boceprevir) (relevant to Key Questions 1a, 1b, 2a, 2b, 3a, and 3b).

6. Need for trials evaluating the boceprevir regimen approved by the FDA in antiviral-naïve patients without baseline cirrhosis (relevant to Key Questions 1a, 1b, 2a, 2b, 3a, and 3b).
7. Need for studies that evaluate the usefulness of genomics and other methods for individualizing treatment decisions in patients with HCV infection (relevant to Key Questions 1b, 2b, and 3b).

**Comparator-Related Gaps:**

8. Need for more studies on clinical outcomes in patients who experience SVR following antiviral treatment versus those who do not experience SVR that are methodologically rigorous, including adequate controlling for potential confounders (relevant to Key Question 4).

**Outcome/Timing-Related Gaps:**

9. Need for studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection (relevant to Key Questions 1a and 1b).
10. Need for methodologically rigorous studies on effects of achieving a SVR on long-term quality of life (relevant to Key Question 4).
11. Need for studies with long-term followup of patients exposed to telaprevir and boceprevir to understand the long-term harms (relevant to Key Questions 3a and 3b).

**Other Issues:**

12. Need for studies not funded by pharmaceutical companies, as almost all studies of antiviral therapies were funded by pharmaceutical companies; studies have found that industry-funded studies tend to report more favorable results than studies not funded by industry (relevant to all Key Questions).

## Methods

We began by generating an initial list of evidence gaps as identified in the CER. The Principal Investigator of this Future Research Needs report also served as the Principal Investigator of the CER and provided insight into the identified future research needs. We reviewed all notes available from Key Informant interviews and Technical Expert Panels discussions undertaken as part of the CER processes. The preliminary list of evidence gaps was supplemented and refined through input from stakeholders selected to represent a variety of perspectives, including clinicians, researchers, policymakers, payers, research funders, and consumer advocates, and was subsequently prioritized into a top-tier list of research needs. This was accomplished through an initial Webinar and phone discussion with stakeholders, followed by two rounds of Web-based prioritization using questionnaires, based on the Delphi method. SurveyMonkey™ was used to create and deliver the surveys and organize stakeholder responses.

For the initial questionnaire, we asked stakeholders to describe their stakeholder perspective(s) and to describe any additional gaps missing from the initial list that they thought were important, within the scope of the original CER. We initially asked the stakeholders to consider the following criteria when ranking gaps as high, medium, or low priority:

- Burden of disease
- High public interest
- Vulnerable populations
- Utilization of existing resources
- Potential impact
- Their own reasoning.

In the second and final questionnaire, we asked the stakeholders to rank the evidence gaps in order of priority, using the Effective Health Care (EHC) Program Selection Criteria to rank clinical importance and significance, which included:

- Appropriateness
- Importance
- Desirability of research/Avoidance of unnecessary duplication
- Feasibility
- Potential impact.

The top five gaps that received the most stakeholder endorsements were to be classified as the top-tier research needs, followed by the second-tier gaps. Any gaps raised by the stakeholders that fell outside the scope of the CER were not prioritized.

For the top-tier research needs, a research librarian then searched the Ovid pre-MEDLINE, MEDLINE, and the Cochrane Central Register of Controlled Trials databases using the search strings developed for the original CER.<sup>1</sup> The searches for the CER were conducted through August 2012. We also searched using National Institute of Health's ClinicalTrials.gov and Current Controlled Trials. We searched for ongoing studies of currently approved treatments or studies of unapproved treatments in phase 3 or 4 of clinical testing conducted in treatment-naïve, HCV-infected individuals. We did not look for studies that would fall outside the scope of the treatment CER, such as studies conducted in treatment-experienced patients, patients with HIV or hepatitis B virus coinfection, or children.<sup>1</sup>

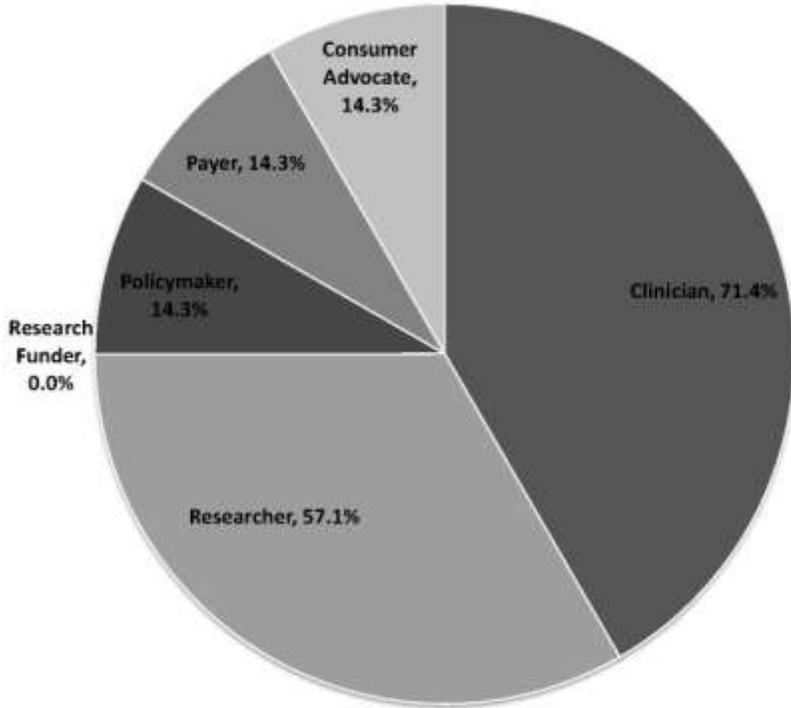
Our research team then proposed study designs to address the top-tier gaps, described research considerations, and provided example research questions with accompanying PICOT specifications.

## Results

Of 14 stakeholders invited to participate in the project, eight agreed to participate. Seven stakeholders completed the first questionnaire and six stakeholders completed the second (final) questionnaire. No participating stakeholders reported significant conflicts of interest that precluded participation, as determined by AHRQ and our team.

The participating stakeholders identified themselves as representing clinicians (71.4%), researchers (57.1%), policymakers (14.3%), payers (14.3%), and consumer advocate (14.3%) stakeholder perspectives (Figure B). Individuals could represent more than one area. While no stakeholder identified themselves as a "research funder," we did include one stakeholder from a Federal agency that funds clinical research. Some may be hesitant to identify themselves as research funders due to concerns that their opinions would be seen as representative of their funding organization.<sup>2</sup>

**Figure B. Stakeholder perspectives**



The final, ranked prioritization of the top-tier research needs are shown in Table A, followed by the second-tier research needs. There were tie scores for the first and fifth place rankings, so instead of the top five needs, our list includes the top seven needs. In addition, there was not a clear demarcation between top-tier and second-tier research needs, and several of the gaps overlapped. In particular, our research team thought that research need #7 (the lack of studies of clinical outcomes among patients who experience SVR that adequately controlled for potential confounders) and research need #8 (the need for rigorous studies conducted in U.S. applicable settings evaluating the association between SVR and improved clinical outcomes) had considerable overlap in terms of scope. Therefore, even though research need #8 is categorized as second tier, we combined it with research need #7 in our discussion of study designs for top-tier research needs.

**Table A. Final prioritization of research needs**

Research Needs	Weighted Score <sup>a</sup>
<b>Top Tier</b>	
1. Need for studies designed using an effectiveness paradigm to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials.	<b>26 (tie score)</b>
2. Lack of studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice, such as advanced cirrhosis and IV drug users.	
3. Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon.	<b>31</b>
4. Lack of studies in screen detected patients.	<b>32</b>
5. Lack of studies on effects of using noninvasive methods for assessing liver fibrosis to guide treatment decisions.	<b>37</b>
6. Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection.	<b>39 (tie score)</b>
7. Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR.	
<b>Second Tier</b>	
8. Need for methodologically rigorous studies conducted in settings applicable to U.S. populations evaluating the association between achieving an SVR and improvements in clinical outcomes.	<b>41</b>
9. Lack of studies evaluating the usefulness of genomics and other methods for individualized treatment decisions in patients with HCV infection using genomics or other methods (e.g., treatment algorithms) and how these treatment decisions affect clinical outcomes.	<b>42</b>
10. Lack of studies enrolling patients with advanced age (>65-70 years).	<b>47</b>
11. Need for well-designed, independently funded studies. Almost all of the randomized trials were funded by pharmaceutical companies. Such studies tend to report more favorable results from drugs produced by the funder than studies funded by governmental or other sources.	<b>50</b>
12. Lack of studies reporting long-term followup of patients exposed to telaprevir and boceprevir to understand the long-term harms associated with use of telaprevir and boceprevir.	<b>58</b>

Note: HCV=hepatitis C virus, IV=intravenous, SVR=sustained virologic response, U.S.=United States.

<sup>a</sup> Weights are based on the rank numbers (1–12) of each gap multiplied by how many stakeholders assigned them a specific rank number. Therefore, the gaps with the lowest scores indicated the highest priority gaps.

We identified 50 ongoing studies that may potentially address a future research need. Among these ongoing studies, three focused on patients with cirrhosis, one enrolled intravenous drug users, four were efficacy trials of new (not yet approved) interferon-free treatment regimens in antiviral-naïve patients, and three evaluated long-term virologic outcomes and harms associated with antiviral treatments. We did not include studies of alisporivir (also known as DEB025), a cyclophilin inhibitor, as research was suspended in April 2012 by the FDA due to safety concerns.<sup>3</sup> We identified no ongoing studies that evaluated long-term clinical outcomes associated with antiviral treatments or that enrolled screen-detected patients. No study clearly was designed using an effectiveness framework, though details on methods were fairly limited. Although the remainder of the ongoing studies enrolled treatment-naïve individuals, they were less relevant to the top-tier research needs. Most studies were short-term, interferon-based efficacy studies with SVR as the primary outcome.

We propose both randomized controlled trials (RCTs) and cohort studies as applicable and ideal study designs for addressing top-tier research needs #1 (effectiveness paradigm), #2 (broader populations), #4 (screen-detected patients), and #6 (important long-term clinical outcomes). For research needs #3 (new drugs) and #5 (comparative effectiveness of liver fibrosis testing), we propose RCTs; and for #7 (controlling for adequate confounders) and #8 (association between achieving an SVR and improvements in clinical outcomes), we propose cohort studies.

We propose the following example research questions utilizing these study designs to address the top-tier research needs:

Research Need #1:

- What is the comparative effectiveness of different antiviral regimens in patients recruited from community settings, using broad inclusion criteria?
- How does the efficacy of antiviral drugs change with lower treatment adherence?

Research Need #2

- How do outcomes of antiviral treatments differ in patients with HCV who are IV drug users versus patients without IV drug use?

Research Need #3

- What is the comparative effectiveness of oral antiviral regimens without interferon for HCV versus interferon-based regimens?

Research Need #4

- How does the efficacy of antiviral treatment for HCV differ in patients identified through screening versus those identified based on symptoms or abnormal liver tests?

Research Need #5

- What is the comparative effectiveness of antiviral treatments in patients selected for therapy based on a liver biopsy versus those selected for treatment without undergoing a liver biopsy?

Research Need #6

- What are the effects of antiviral therapy on clinical outcomes in patients at higher risk for disease progression?

Research Needs #7 and #8

- How do outcomes differ among U.S. patients with HCV infection who experience an SVR versus those who do not experience an SVR after antiviral therapy?

## Discussion

Based on the 2012 CER, and with the input of stakeholders, we identified 12 evidence gaps, seven of which were prioritized as top-tier research needs, and the remainder as second-tier research needs based on the priority rankings of stakeholders. Most of the research gaps did not suggest new research questions to be addressed; rather they primarily identified the need for more applicable and methodologically rigorous studies. In fact, a number of the research gaps (such as the need for studies that evaluate an effectiveness paradigm, studies that evaluate patients with important comorbidities, and studies that are not funded by the pharmaceutical industry) are relevant across many research questions applicable to understanding the comparative effectiveness of antiviral treatments for HCV. Nonetheless, we suggested specific research questions that could address each of these needs.

A limitation of our report is the omission of potentially important research needs due to the requirement of the needs to be within the scope of the original CER. For example, the CER did not evaluate patients with HIV or hepatitis B virus coinfection, or patients who had previously been treated for HCV infection. It also excluded children. Because the CER did not evaluate the state of the evidence for these populations, the extent of research gaps and availability of research was not known. Such areas could be the subject of nominations for future CERs in the EHC program. The precedent for this limitation was initially discussed with the stakeholders during the webinar, which precluded any out of scope gaps from being raised at subsequent opportunities.

Another limitation is that we also had a small sample of stakeholders, with limited representation of some stakeholder perspectives. In addition, standardized and validated methods for selecting stakeholders and synthesize diverse stakeholder viewpoints are not yet available, but would be helpful for Future Research Needs projects.

The rapidly evolving nature of antiviral HCV treatments suggests that even a CER completed this year will need to be updated in the near future. Stakeholders emphasized that all-oral, interferon-sparing regimens are expected within the next few years and will likely have a major impact on clinical practice.

## **Conclusions**

Future research needs as prioritized by a stakeholder group representing diverse perspectives focused on the need for more methodologically rigorous and applicable research to better understand the comparative effectiveness of antiviral treatments for HCV infection in antiviral-naïve patients. Clinical trials of all-oral, interferon-sparing regimens are ongoing and illustrate the rapidly evolving nature of HCV treatments.

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# Background

## Context

Future Research Needs reports are intended to inform and support researchers and those who fund research to ultimately enhance the body of comparative effectiveness evidence so that it is useful for decisionmakers. This Future Research Needs report focuses on developing and prioritizing the most pressing research needs around antiviral treatment of hepatitis C virus (HCV) infection in adults.

HCV is the most common chronic blood-borne pathogen in the United States (U.S.). HCV is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use the strongest risk factor. Based on a national survey of households, approximately 1.6 percent of U.S. adults over 20 years of age have antibodies to HCV, indicating prior acute HCV infection.<sup>1</sup> About 78 percent of patients with acute HCV infection develop chronic HCV infection, defined by the presence of persistent viremia.

Chronic HCV infection has a variable course, but it is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular cancer. Chronic HCV infection is associated with an estimated 15,000 deaths each year in the U.S.,<sup>2</sup> and it is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases.<sup>3</sup> The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people and the yearly incidence has declined from more than 200,000 cases per year in the 1980s to around 16,000 cases in 2009.<sup>4, 5</sup> However, complications related to chronic HCV infection, which frequently occur only after decades of infection, are expected to rise for another 10 to 13 years.<sup>4</sup>

The goals of antiviral treatment for chronic HCV infection are to prevent the long-term health complications associated with HCV infection such as cirrhosis, hepatic decompensation, and liver cancer, but it is extremely difficult to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The sustained virologic response (SVR) rate, typically defined as a decline in HCV RNA to undetectable levels 24 weeks following completion of antiviral treatment, is the standard marker of successful treatment in clinical trials because it is strongly associated with long-term absence of viremia.<sup>6, 7</sup> Recent studies have evaluated the association between achieving an SVR and reductions in mortality, liver failure, and cancer.<sup>8, 9</sup>

In the early 2000s, the combination of “pegylated” interferon plus ribavirin became the standard antiviral treatment for HCV infection.<sup>10-12</sup> Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance and thereby permits less frequent dosing (once weekly vs. three times a week with standard interferon).<sup>13</sup> Dual therapy with pegylated interferon plus ribavirin is associated with higher SVR rates (about 55 to 60 percent overall) than either standard interferon plus ribavirin or pegylated interferon monotherapy. Currently, two pegylated interferons are available: pegylated interferon alfa-2a and pegylated interferon alfa-2b. Although previous reviews found insufficient evidence to determine whether combination therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b plus ribavirin is more effective,<sup>14, 15</sup> more head-to-head trials directly comparing these two regimens are now available.<sup>16-19</sup>

A number of factors affect response to antiviral treatment. The two major pretreatment predictors of SVR are the viral genotype and the pretreatment viral load.<sup>11</sup> In the U.S., genotype 1 infection is found in around three-quarters of HCV-infected patients.<sup>20</sup> HCV genotype 1

infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20 percent of HCV-infected patients. A pretreatment viral load of <600,000 IU/mL is associated with higher likelihood of achieving an SVR.<sup>11</sup> Other factors less consistently or less strongly associated with increased likelihood of SVR include female sex, age less than 40 years, non-African-American race, lower body weight ( $\leq 75$  kg), absence of insulin resistance, elevated alanine aminotransferase levels, and absence of bridging fibrosis or cirrhosis on liver biopsy.<sup>11</sup> Effects of race on the likelihood of SVR may be due in part to polymorphisms in the interleukin-28B (IL28B) gene.<sup>21, 22</sup>

An issue complicating antiviral treatment is the high rate of adverse effects observed with interferon-based therapy, including flu-like symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.<sup>23</sup> Such adverse effects can be difficult to tolerate and can lead to premature discontinuation of therapy.

In 2011, the U.S. Food and Drug Administration (FDA) approved the first direct acting antiviral agents, boceprevir (trade name Victrelis<sup>®</sup>) and telaprevir (trade name Incivek<sup>®</sup>), for treatment of chronic HCV genotype 1 infection.<sup>24, 25</sup> Both drugs are classified as nonstructural 3/4A protease inhibitors, with a potential advantage of shorter duration of therapy (24 to 28 weeks) compared with standard dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin for genotype 1 infection (48 weeks).<sup>26-28</sup> Either drug is administered in combination with pegylated interferon (alfa-2a or 2b) plus ribavirin.

## Findings From Comparative Effectiveness Review

In 2010 the Agency for Healthcare Research and Quality (AHRQ) charged the Oregon Evidence-based Practice Center (EPC) with conducting a Comparative Effectiveness Review (CER)<sup>29</sup> on antiviral treatments for HCV infection. The CER will be published in 2012 and searches for the review were conducted through August, 2012. The CER focused on current FDA-approved antiviral therapies for antiviral-naïve adults with chronic HCV infection, without HIV or hepatitis B virus coinfection.

The Key Questions addressed in the CER were:

### Key Question 1:

- 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
- 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

### Key Question 2:

- 2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?
- 2b. 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:

- 3a. What are the comparative harms associated with antiviral treatments?

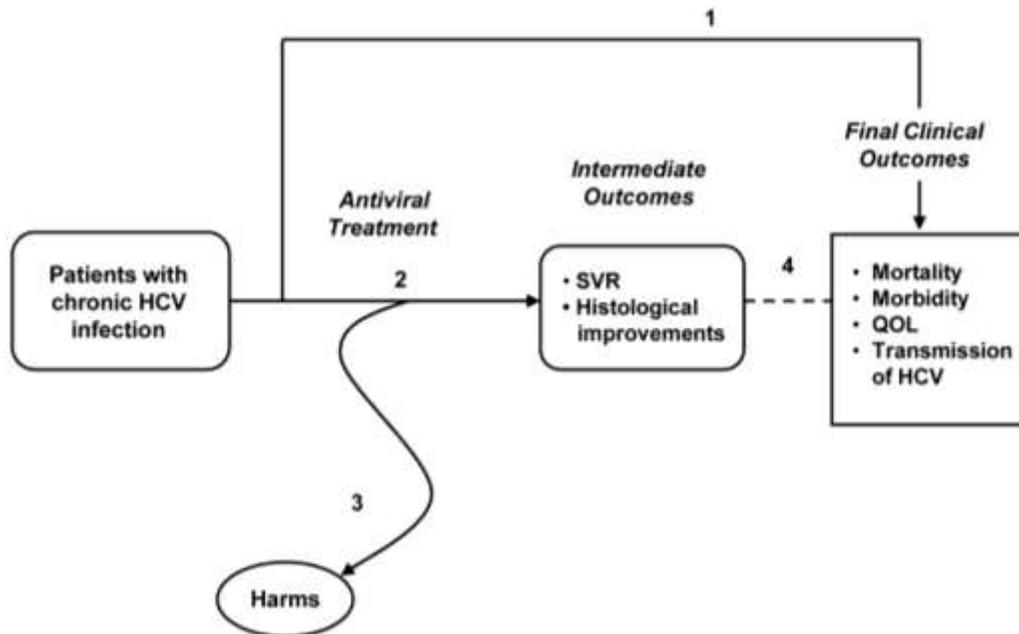
3b. Do these harms differ according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

### Key Question 4:

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

The analytic framework (Figure 1) illustrates the targeted population, interventions, and outcomes for the CER. The numbers in the figure refer to the numbers of the Key Questions.

**Figure 1. Analytic framework from Comparative Effectiveness Review**



Note: HCV=hepatitis C virus, QOL=quality of life, SVR=sustained virologic response.

The objectives of the CER were to understand the comparative benefits and harms of the various antiviral regimens to make informed treatment decisions in antiviral-naïve patients with chronic HCV infection, particularly given the availability of new treatment options. The review assessed the comparative effectiveness of antiviral treatments in adults with chronic HCV infection who have not received previous antiviral drug treatment. In addition to assessing the comparative effectiveness of different drug regimens, the review evaluated effects of different medication doses, durations of therapy, and dosing strategies (such as weight-based or response-guided vs. fixed treatment), and how comparative effectiveness varies depending on HCV genotype, viral load, and other demographic and clinical characteristics. The CER did not evaluate antiviral treatment of HCV-infected patients with HIV or hepatitis B coinfection, pregnant women, or children.

The results of the CER are summarized in the Summary of Evidence table (Table 1).

**Table 1. Summary of evidence table from the comparative effectiveness review**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
<b>Key Question 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?</b>	<b>Long-term clinical outcomes</b>	No evidence.	Insufficient
	<b>Short-term mortality</b>	Three trials that compared current antiviral regimens <sup>a</sup> found no differences in risk of short-term mortality, but reported few (20 total) events.	Low
	<b>Short-term quality of life</b>	One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with statistically significant, slightly better short-term scores on some quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin.	Low

**Table 2. Summary of evidence table from the comparative effectiveness review (continued)**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
<b>Key Question 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?</b>	<b>Any clinical outcome</b>	No evidence.	Insufficient

**Table 3. Summary of evidence table from the comparative effectiveness review (continued)**

Key Question	Outcome	Summary of Evidence	Strength of Evidence
<b>Key Question 2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes?</b>	<b>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin</b>		
	<b>Sustained virologic response</b>	Seven trials found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI, 0.80 to 0.95; $I^2=27%$ ), with an absolute difference in SVR rates of 8 percentage points (95% CI, 3 to 14).	Moderate
	<b>Dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin: duration effects</b>		
	<b>Sustained virologic response</b>	Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI, 0.84 to 1.1; $I^2=43%$ ).	Moderate
	<b>Sustained virologic response</b>	Four trials of patients with genotype 2 or 3 infection found 24 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) more effective than 12-16 weeks for achieving an SVR (pooled RR 1.2, 95% CI, 1.0 to 1.3; $I^2=80%$ ). Relative risk estimates ranged from 1.0 to 1.3 in the four trials and may have varied in part due to differences across studies in ribavirin dosing.	Moderate
	<b>Sustained virologic response</b>	Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences between 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR 0.99, 95% CI, 0.86 to 1.1, $I^2=66%$ ). Relative risk estimates ranged from 0.89 to 1.1.	Moderate
	<b>Dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin: dose effects</b>		
	<b>Sustained virologic response</b>	Six trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.90; 95% CI, 0.81 to 0.99; $I^2=20%$ ).	Moderate
	<b>Sustained virologic response</b>	Three 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 between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. higher doses (800 or 1,200 mg flat dose or 800 to 1400 mg weight-based dose).	Moderate
	<b>Sustained virologic response</b>	One small trial of patients with genotype 2 or 3 infection (n=97) and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 600 to 800 mg daily of ribavirin associated with lower likelihood of SVR than 1000 to 1200 mg daily (45 vs. 72 percent, RR 0.62, 95% CI, 0.40 to 0.98).	Low
	<b>Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin</b>		
	<b>Sustained virologic response</b>	Two trials of patients with genotype 1 infection found triple therapy with boceprevir (pegylated interferon alfa-2b plus ribavirin for 4 weeks, followed by the addition of boceprevir for 44 weeks) associated with higher likelihood of SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin therapy for 48 weeks (pooled RR 1.8; 95% CI, 1.6 to 2.1; $I^2=0%$ ), with an absolute increase in SVR rate of 31% (95% CI, 23 to 39).	Moderate

	<b>Sustained virologic response</b>	One trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1000 mg daily) associated with a non-statistically significant trend toward lower likelihood of SVR compared with 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs. 50%, RR 0.71, 95% CI, 0.39 to 1.3).	Low
	<b>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</b>		
	<b>Sustained virologic response</b>	Three trials of patients with genotype 1 infection found 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) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI, 1.3 to 1.8; I <sup>2</sup> =0%), with an absolute increase in SVR rate of 22% (95% CI, 13 to 31).	Moderate
	<b>Sustained virologic response</b>	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Moderate
	<b>Sustained virologic response</b>	One trial of patients with genotype 1 infection found 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) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI, 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25% to 31%. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%).	Low
	<b>Sustained virologic response</b>	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between 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).	Low
	<b>Triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir: dose effects of pegylated interferon alfa-2a vs. -2b and duration effects</b>		
	<b>Sustained virologic response</b>	One 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. 1125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b).	Low
	<b>Sustained virologic response</b>	One 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.	Low

**Table 4. Summary of evidence table from the comparative effectiveness review (continued)**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
<b>Key Question 2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?</b>	<b>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin</b>		
	<b>Sustained virologic response</b>	The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin 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 across dual therapy regimens were older age, Black race, advanced fibrosis or cirrhosis, and high baseline viral load.	Low
	<b>Sustained virologic response</b>	Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype. Genotype 1 infection was associated with a lower absolute SVR rate than genotypes 2 or 3.	Moderate
	<b>Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin</b>		
	<b>Sustained virologic response</b>	Two trials of 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, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men vs. women, and no clear difference in relative risk estimates for Black vs. non-Black patients. Black race was associated with a lower absolute SVR rate than non-Black race.	Moderate

**Table 5. Summary of evidence table from the comparative effectiveness review (continued)**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
	<b>Sustained virologic response</b>	Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir associated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV-RNA viral load (>600,000 or $\geq$ 800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load.	Moderate
	<b>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</b>		
	<b>Sustained virologic response</b>	One trial of 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 found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index. Characteristics associated with lower absolute rates of SVR were older age, Black race, advanced fibrosis or cirrhosis, and higher body mass index. One other trial of 24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy found no differences in estimates of effect in patients stratified by sex or age.	Moderate (for age and sex) Low (for other factors)
	<b>Sustained virologic response</b>	Two trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy depending reported inconsistent findings for differential relative risk estimates according baseline viral load.	Insufficient

**Table 6. Summary of evidence table from the comparative effectiveness review (continued)**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
<b>Key Question 3a. What are the comparative harms associated with antiviral treatments?</b>	<b>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin</b>		
	<b>Harms</b>	Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (three trials, pooled RR 1.1, 95% CI, 1.1 to 1.2, $I^2=0\%$ ), and a lower risk of serious adverse events (two trials, pooled RR 0.74; 95% CI, 0.57 to 0.95; $I^2=0\%$ ), lower risk of neutropenia (five trials, pooled RR 0.60, 95% CI, 0.46 to 0.83), and lower risk of rash (two trials, pooled RR 0.79, 95% CI, 0.71 to 0.88, $I^2=0\%$ ) than dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in withdrawals due to adverse events.	Moderate
	<b>Triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir vs. dual therapy with pegylated interferon alfa-2b plus ribavirin</b>		
	<b>Harms</b>	Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) was associated with increased risk of neutropenia (two trials, pooled RR 1.8, 95% CI, 1.5 to 2.3, $I^2=0\%$ ), dysgeusia (two trials, pooled RR 2.5, 95% CI, 2.0 to 3.2, $I^2=0\%$ ), anemia (two trials, pooled RR 2.0, 95% CI, 1.4 to 2.8, $I^2=0\%$ ), and thrombocytopenia (two trials, pooled RR 3.3, 95% CI, 1.3 to 8.6) than dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 50% with triple therapy and the incidence of neutropenia about 25%, with severe anemia in 4–5% and severe neutropenia in 8–15%.	Moderate
	<b>Triple therapy with pegylated interferon alfa (-2a or -2b), ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa(-2a or -2b) plus ribavirin</b>		
	<b>Harms</b>	In two trials, there were no statistically significant differences between a 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event.	Moderate

**Table 7. Summary of evidence table from the comparative effectiveness review (continued)**

<b>Key Question</b>	<b>Outcome</b>	<b>Summary of Evidence</b>	<b>Strength of Evidence</b>
	<b>Harms</b>	In three trials, a 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) was associated with increased risk of anemia (three trials, pooled RR 1.3, 95% CI, 1.1 to 1.5, $I^2=0\%$ ) and rash (three trials, pooled RR 1.4, 95% CI, 1.1 to 1.7) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks. Among patients randomized to the 24-week telaprevir regimen, one to two-thirds experienced a rash (7–10% experienced severe rash) and 27–91% experienced anemia (4–11% experienced severe anemia). There was no difference in risk of withdrawal due to adverse events.	Moderate
	<b>Harms</b>	In one trial, 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) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI, 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI, 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5, 95% CI, 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI, 1.6 to 13) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Low
<b>Key Question 3b. Do these harms differ according to patient subgroup characteristics?</b>	<b>Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin</b>		
	<b>Harms</b>	No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three 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.	Insufficient
	<b>Triple therapy with pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir or boceprevir vs. dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin</b>		
	<b>Harms</b>	No trial evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection.	Insufficient

**Table 8. Summary of evidence table from the comparative effectiveness review (continued)**

Key Question	Outcome	Summary of Evidence	Strength of Evidence
<b>Key Question 4. Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?</b>	<b>Mortality and long-term hepatic complications</b>	A large VA hospital study that controlled well for potential confounders found an SVR after antiviral therapy associated with lower risk of all-cause mortality vs. no SVR (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). Eighteen other cohort studies found an SVR associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD compared with no SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 10 were conducted in Asia.	Moderate
	<b>Short-term quality of life</b>	Nine studies found an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment vs. no SVR, with differences averaging less than 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 followup, and failure to blind patients to SVR status.	Low

Note: CI=confidence interval, ESLD=end-stage liver disease, HCC=hepatocellular carcinoma, HCV=hepatitis C virus, HCV-RNA=hepatitis C virus ribonucleic acid, HR=hazard ratio;  $I^2$ =index measures the extent of true heterogeneity in a meta-analysis, RR=relative risk, SF-36= short-form health survey with 36 questions, SVR=sustained virologic response, VA=Veterans Affairs. “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.

Research gaps and limitations of the existing literature identified in the CER are summarized below, organized according to the most relevant elements of the population, intervention, comparator, outcome, and timing (PICOT) framework. Important contextual issues noted in the CER are also described.

## Evidence Gaps From Comparative Effectiveness Review

We organized the evidence gaps from the CER according to the PICOT framework:

### Population-Related Gaps:

1. Need for studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice (relevant to all Key Questions).
2. Need for studies of treatment in screen-detected patients, to understand applicability to this population (relevant to all Key Questions).
3. Need for studies designed using an effectiveness paradigm, to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than observed in efficacy trials (relevant to all Key Questions).
4. Need for studies on effects of newer triple therapy regimens with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors (relevant to Key Questions 2b, 3b).

### Intervention-Related Gaps:

5. Need for head-to-head studies comparing triple therapy with newer protease inhibitors (telaprevir and boceprevir) (relevant to Key Questions 1a, 1b, 2a, 2b, 3a, and 3b).

6. Need for trials evaluating the boceprevir regimen approved by the FDA in antiviral-naïve patients without baseline cirrhosis (relevant to Key Questions 1a, 1b, 2a, 2b, 3a, and 3b).
7. Need for studies that evaluate the usefulness of genomics and other methods for individualizing treatment decisions in patients with HCV infection are also needed (relevant to Key Questions 1b, 2b, and 3b).

**Comparator-Related Gaps:**

8. Need for more studies on clinical outcomes in patients who experience SVR following antiviral treatment versus those who do not experience SVR that are methodologically rigorous, including adequate controlling for potential confounders (relevant to Key Question 4).

**Outcome/Timing-Related Gaps:**

9. Need for studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection (relevant to Key Questions 1a and 1b).
10. Need for methodologically rigorous studies on effects of achieving a SVR on long-term quality of life (relevant to Key Question 4).
11. Need for studies with long-term followup of patients exposed to telaprevir and boceprevir to understand the long-term harms (relevant to Key Questions 3a and 3b).

**Other Issues:**

12. Need for studies not funded by pharmaceutical companies, as almost all studies of antiviral therapies were funded by pharmaceutical companies; studies have found that industry-funded studies tend to report more favorable results than studies not funded by industry (relevant to all Key Questions).

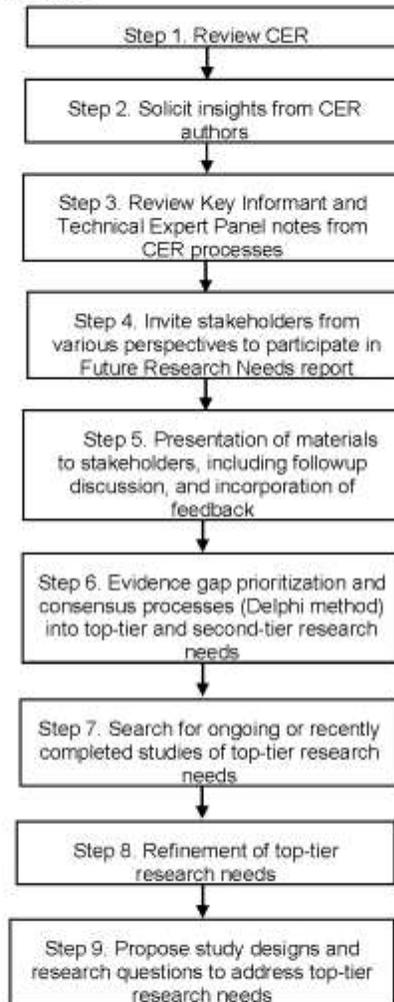
## **Known Ongoing Research From Comparative Effectiveness Review**

A number of other protease inhibitors and other newer drugs for treatment of HCV infection are currently in active development and further studies with new drugs and drug regimens are expected, including all-oral, interferon-sparing regimens.<sup>30</sup>

## **Methods**

The specific steps used for this Future Research Needs report on antiviral treatment of HCV infection in adults are depicted and described in the flow diagram (Figure 2).

**Figure 2. Flow diagram of methods**



**Note:** CER = Comparative Effectiveness Review.

## Identification of Evidence Gaps

We began by generating an initial list of evidence gaps as identified in the CER. The Principal Investigator of this Future Research Needs report also served as the Principal Investigator of the CER and provided insight into the identified future research needs. We reviewed all notes available from Key Informant interviews and Technical Expert Panel discussions undertaken as part of the CER processes. Stakeholder input was then solicited and used to identify additional evidence gaps, which were also organized around the PICOT framework, and subsequently prioritized into a top-tier list of research needs. This was accomplished through an initial Webinar and phone discussion with stakeholders, followed by two rounds of Web-based prioritization using stakeholder questionnaires, based on the Delphi method. SurveyMonkey™ was used to create and deliver the surveys and organize stakeholder responses. The top five gaps that received the most stakeholder endorsements were to be classified as the top-tier research needs, followed by the second-tier gaps. Gaps raised by the stakeholders that fell outside the scope of the CER were not prioritized, but are discussed.

## Criteria for Prioritization

After establishing a list of potential evidence gaps, the research team developed two prioritization questionnaires, which were tested internally for clarity and ease of use.

For the initial questionnaire (available in Appendix A), we asked the stakeholders to consider the following criteria when ranking gaps as high, medium, or low priority:

- Burden of disease
- High public interest
- Vulnerable populations
- Utilization of existing resources
- Potential impact
- Their own, additional reasoning.

We also asked stakeholders to describe their stakeholder perspective(s) and to describe any additional gaps missing and that they thought were most important.

In the second and final questionnaire (available in Appendix B), we asked the stakeholders to rank the evidence gaps in order of priority, using the Effective Health Care (EHC) Program Selection Criteria to help rank clinical importance/significance. The EHC Program Selection Criteria include the following:

### **Appropriateness:**

- Represents a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States.
- Relevant to 1,013 enrollees (Medicare, Medicaid, State Children's Health Insurance Program [SCHIP], other Federal health care programs).
- Represents one of the priority conditions designated by the U.S. Department of Health and Human Services.

### **Importance:**

- Represents a significant disease burden, large proportion or priority population.
- Is of high public interest; affects health care decisionmaking, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular.

- Was nominated/strongly supported by one or more stakeholder groups.
- Represents important uncertainty for decisionmakers.
- Incorporates issues around both clinical benefits and potential clinical harms.
- Represents important variation in clinical care or controversy in what constitutes appropriate clinical care.
- Represents high costs to consumers, patients, health care systems or payers due to common use, high unit costs, or high associated costs.

**Desirability of New Research/Duplication:**

- 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 the AHRQ or others).

**Feasibility:**

- Effectively uses existing research and knowledge by considering adequacy of research for conducting a systematic review and newly-available evidence.

**Potential Impact:**

- Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups.

We used the Delphi method for prioritization and consensus. In the Delphi method, input is sought from all stakeholders and information derived from prior communications is included in subsequent prioritization steps; therefore all stakeholders receive equal representation in the prioritization and consensus process. We decided a priori that prioritization would be repeated for no more than three rounds. For the initial round, we weighted the scores based on how many stakeholders endorsed the gap multiplied by a score based on the priority category high=3, medium=2, low=1, and then the gaps were ordered highest score to lowest score. The gaps with high and medium scores ( $\geq 14$  out of a possible 21) were included in the next survey and gaps with lower scores were removed from further prioritization. For the next round, each stakeholder ranked the remaining priorities from highest priority (1) to lowest priority. The final prioritization was based on the total priority score, which was the sum of priority scores across all stakeholders. The research gaps with the lowest scores indicated the highest priority gaps. We did not conduct a third round of prioritization because the second round identified a sufficient number of research needs that received higher priority scores, using a cut-off score of 40. These top five gaps were to become the tier one research needs, and the remaining gaps were to be classified as second-tier research needs.

## **Search for Ongoing or Recently Completed Studies**

For the top-tier research needs, a research librarian searched the Ovid pre-MEDLINE, MEDLINE, and the Cochrane Central Register of Controlled Trials databases using the search strings developed for the original CER (Appendix C). The searches for the CER were conducted through August 2012. The librarian also searched for ongoing studies relevant to the identified research gaps using ClinicalTrials.gov and Current Controlled Trials.

## **Engagement of Stakeholders From Various Perspectives**

We engaged stakeholders from a variety of perspectives to identify important evidence gaps and prioritize future research needs. Stakeholders included a mix of both non-Federal and Federal clinicians, researchers, research funders, policymakers, payers, and consumer advocates. We attempted to have at least one stakeholder represent each of these perspectives on the panel, while ensuring that the panel included clinicians and researchers with the expertise and background to understand and evaluate the evidence gaps. Some stakeholders also served as Key Informants and Technical Experts for the CER. We submitted a list of proposed stakeholders to AHRQ. Following approval by AHRQ, we invited stakeholders to participate via email solicitations. Stakeholders who agreed to participate submitted conflict of interest statements. Conflicts of interest were evaluated and subject to approval by both our team and AHRQ.

In addition, we submitted the project protocol to the Oregon Health & Science University Institutional Review Board (IRB). The IRB reviewed and authorized the project to proceed as exempt from human subject research.

We hosted a Web-based presentation and conference call (Webinar) to orient stakeholders to the project and the major findings, limitations, and research gaps identified in the CER. The full text of the CER, the slides for the presentation, and orientation materials were sent to stakeholders prior to the phone meeting. Following the presentation, we facilitated a discussion among the stakeholders to generate a list of additional research gaps and to gain feedback on the previously identified gaps. We requested specific feedback for each domain of the PICOT framework, and provided time for additional open-ended feedback. Following the Webinar and associated discussion, we circulated questionnaires to the stakeholders to collect thoughts on current and additional gaps, as well as input on prioritization.

The Future Research Needs report will be publically posted for a period of 4 weeks, during which anyone can provide feedback. The stakeholders will be informed of the posting period.

## **Research Design Considerations and Research Questions**

As a final step, our research team proposed study designs to address the top research needs using a recent study design guidance framework.<sup>31</sup> We considered the following factors at this final phase:

- Ability to produce a valid result
- Resource use
- Ethical factors
- Data availability
- Recruitment feasibility

We also provided example research questions and accompanying PICOT specifications.

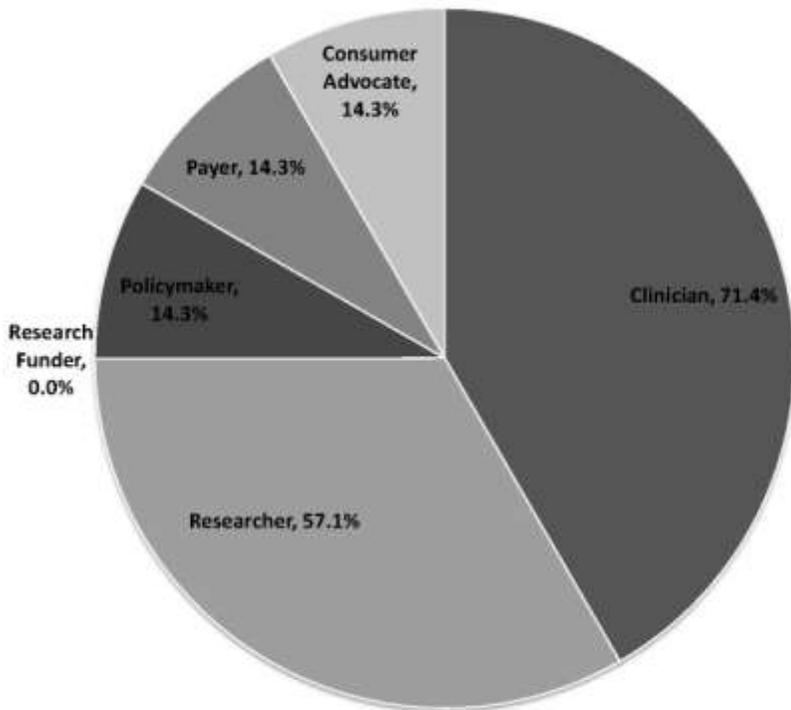
# Results

## Stakeholders

Of 14 stakeholders invited to participate in the project, eight agreed to participate, four declined, and two did not respond to invitations. Of the eight that agreed to participate, six attended the Webinar and followup discussion, while one stakeholder could not attend the Webinar but participated in followup surveys. Another stakeholder did not contribute to the prioritization process due to inability to participate in the Webinar or in subsequent surveys. No participating stakeholders reported significant conflicts of interest that precluded participation, as determined by AHRQ and our team.

All seven stakeholders who were invited to complete the questionnaires returned the first questionnaire and six returned the second (final) questionnaire. The participating stakeholders identified themselves as representing different perspectives, including clinicians, researchers, policymakers, payers, and consumer advocates. Individuals could represent more than one area. While no stakeholder identified themselves as a “research funder,” we did include one stakeholder from a Federal agency that funds clinical research. Some stakeholders may be hesitant to self-identify as research funders due to concerns that their opinions would be seen as representative of their funding organization.<sup>32</sup> The proportions of self-identified stakeholder perspectives that contributed to this report by either providing feedback via the Webinar and/or questionnaires are illustrated in Figure 3.

Figure 2. Stakeholder perspectives



## Research Needs

### Generated List of Evidence Gaps From Webinar Discussion

As a result of the Webinar discussion, two additional evidence gaps that fell within the scope of the original CER were added to the list of gaps from the CER:

- Lack of studies enrolling patients with advanced age (>65-70 years)
- Lack of studies on effects of using noninvasive methods for assessing liver fibrosis to guide treatment decisions.

The Webinar participants also gave feedback on the list of gaps identified in the original CER. Stakeholders were advised to limit their comments to gaps that would fall within the scope of the CER, so little time was spent discussing gaps outside this scope (e.g., the lack of studies in children).

### Initial Prioritization of Evidence Gaps

We circulated 15 research gaps for initial prioritization. All seven stakeholders completed the survey. Results are shown in Table 2.

**Table 9. Initial prioritization of evidence gaps**

<b>Research Gap</b>	<b>Number of “High-Priority” Endorsements</b>	<b>Number of “Medium-Priority” Endorsements</b>	<b>Number of “Low-Priority” Endorsements</b>	<b>Weighted Total<sup>a</sup></b>
Lack of studies in screen detected patients.	6	0	1	19
Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon.	6	0	1	19
Need for methodologically rigorous studies conducted in settings applicable to U.S. populations evaluating the association between achieving an SVR and improvements in clinical outcomes.	5	1	1	18
Need for studies designed using an effectiveness paradigm to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials.	5	2	0	19
Lack of studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice, such as advanced cirrhosis and IV drug users.	4	3	0	18
Lack of studies on effects of using noninvasive methods for assessing liver fibrosis to guide treatment decisions.	4	2	1	17

**Table 10. Initial prioritization of evidence gaps (continued)**

<b>Research Gap</b>	<b>Number of “High-Priority” Endorsements</b>	<b>Number of “Medium-Priority” Endorsements</b>	<b>Number of “Low-Priority” Endorsements</b>	<b>Weighted Total<sup>a</sup></b>
Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection.	4	3	0	18
Need for well-designed, independently funded studies. Almost all of the randomized trials were funded by pharmaceutical companies. Such studies tend to report more favorable results from drugs produced by the funder than studies funded by governmental or other sources.	4	3	0	18
Lack of studies evaluating the usefulness of genomics and other methods for individualized treatment decisions in patients with HCV infection using genomics or other methods (e.g., treatment algorithms) and how these treatment decisions affect clinical outcomes.	3	2	2	15
Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR.	3	3	1	16
Lack of studies reporting long-term followup of patients exposed to telaprevir and boceprevir to understand the long-term harms associated with use of telaprevir and boceprevir.	3	4	0	17
Lack of studies enrolling patients with advanced age (>65-70 years).	2	3	2	14
Need for well-conducted studies on the effects of achieving an SVR on long-term quality of life.	1	3	3	12
Lack of head-to-head studies comparing triple therapy regimens (telaprevir or beceprevir + pegylated interferon + ribavirin) with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors.	0	3	4	10
Need for additional trials evaluating the boceprevir regimen by the FDA in antiviral-naïve patients without baseline cirrhosis, to verify that results from studies of previously treated patients were appropriately generalized.	0	5	2	12

Note: FDA=U.S. Food and Drug Administration, HCV=hepatitis C virus, IV=intravenous, SVR=sustained virologic response, U.S.=United States.

<sup>a</sup> Weights are based on the score (high=3, medium=2, low=1) multiplied by the number of stakeholder endorsements.

## Final Prioritization of Research Needs

The final, ranked prioritization of the top research needs is shown in Table 3, followed by the second-tier research needs. Six of the seven stakeholders completed the final prioritization questionnaire. There were tie scores for the first and fifth place rankings, so instead of the top five needs, our list includes the top seven needs. In addition, there was not a clear demarcation between top-tier and second-tier research needs, and several of the gaps overlapped. In particular, our research team thought that research need #7 (the lack of studies of clinical outcomes among patients who experience SVR that adequately controlled for potential confounders) and research need #8 (the need for rigorous studies conducted in U.S. applicable settings evaluating the association between SVR and improved clinical outcomes) had considerable overlap in terms of scope. Therefore, even though research need #8 is categorized as second tier, we combined it with research need #7 in our discussion of study designs for top-tier research needs.

**Table 11. Final prioritization of research needs**

Research Needs	Weighted Score <sup>a</sup>
<b>Top Tier</b>	
1. Need for studies designed using an effectiveness paradigm to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials.	<b>26 (tie score)</b>
2. Lack of studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice, such as advanced cirrhosis and IV drug users.	
3. Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon.	<b>31</b>
4. Lack of studies in screen detected patients.	<b>32</b>
5. Lack of studies on effects of using noninvasive methods for assessing liver fibrosis to guide treatment decisions.	<b>37</b>
6. Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection.	<b>39 (tie score)</b>
7. Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR.	
<b>Second Tier</b>	
8. Need for methodologically rigorous studies conducted in settings applicable to U.S. populations evaluating the association between achieving an SVR and improvements in clinical outcomes.	<b>41</b>
9. Lack of studies evaluating the usefulness of genomics and other methods for individualized treatment decisions in patients with HCV infection using genomics or other methods (e.g., treatment algorithms) and how these treatment decisions affect clinical outcomes.	<b>42</b>
10. Lack of studies enrolling patients with advanced age (>65–70 years).	<b>47</b>
11. Need for well-designed, independently funded studies. Almost all of the randomized trials were funded by pharmaceutical companies. Such studies tend to report more favorable results from drugs produced by the funder than studies funded by governmental or other sources.	<b>50</b>
12. Lack of studies reporting long-term followup of patients exposed to telaprevir and boceprevir to understand the long-term harms associated with use of telaprevir and boceprevir.	<b>58</b>

Note: HCV=hepatitis C virus, IV=intravenous, SVR=sustained virologic response, U.S.=United States.

<sup>a</sup> Weights are based on the rank numbers (1-12) of each gap multiplied by how many stakeholders assigned them a specific rank number. Therefore, the gaps with the lowest scores indicated the highest priority gaps.

## Ongoing and Recently Published Studies

The authors of the original CER reviewed 2,890 citations for potential inclusion. Of those, 77 studies were ultimately included in the final report. Update searches conducted in August, 2012 identified an additional 433 citations, none of which met criteria for inclusion in the CER. In addition to the updated search of Ovid MEDLINE and other bibliographic databases discussed

above, we searched the National Institute of Health’s ClinicalTrials.gov in September 2012 for potentially relevant ongoing studies. As a result of that search, we identified 50 studies that may potentially address a future research need (Appendix D). We searched for studies of currently approved treatments as well of studies of treatments not currently approved, but in phase 3 or 4 of clinical testing. We focused on identifying *ongoing* studies (rather than completed studies or terminated studies) conducted in treatment-naïve, HCV-infected individuals. We did not look for studies that would fall outside the scope of the treatment CER, such as studies conducted in treatment-experienced patients, patients with HIV or hepatitis B virus coinfection, or children.<sup>29</sup>

Table 4 lists ongoing trials most relevant to the top-tier future research needs, and a complete list of all identified ongoing trials is shown in Appendix D. Three ongoing trials focused on patients with cirrhosis, one enrolled intravenous drug users, four were efficacy trials of new (not yet approved) interferon-free treatment regimens in antiviral-naïve patients, and three evaluated long-term virologic outcomes and harms associated with antiviral treatments. We did not include studies of alisporivir (also known as DEB025), a cyclophilin inhibitor, as research was suspended in April 2012 by the FDA due to safety concerns.<sup>33</sup> We identified no ongoing studies evaluating long-term clinical outcomes associated with antiviral treatments or that enrolled screen-detected patients. No study clearly was designed using an effectiveness framework, though details on methods were fairly limited.

Although many other ongoing studies enrolled treatment-naïve individuals, they were less relevant to the top-tier research needs. Most studies were short-term (3 to 6 months followup after completion of antiviral therapy), interferon-based efficacy studies with SVR as the primary outcome.

**Table 12. Selected ongoing studies addressing future research needs**

Future Research Need	Study Titles	Relevant Planned Outcomes <sup>a</sup>
Need for studies designed using an effectiveness paradigm to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials.	No studies identified.	Not applicable.

**Table 13. Selected ongoing studies addressing future research needs (continued)**

Future Research Need	Study Titles	Relevant Planned Outcomes <sup>a</sup>
Lack of studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice, such as advanced cirrhosis and IV drug users.	NCT01609049: Open-label, multicenter, noncomparative, prospective observational study to evaluate efficacy and safety of combined ribavirin and peginterferon alfa-2a (40 kDa) therapy in patients with chronic hepatitis C (CHC) and compensated liver cirrhosis in real clinical practice.	SVR. Adverse events.
	NCT01516918: A multicenter, open-label phase 2b pilot study to evaluate the efficacy and safety of quadruple therapy (VX-222, Telaprevir, Peginterferon-Alfa-2, and Ribavirin) in subjects with genotype 1 chronic hepatitis C with compensated cirrhosis.	SVR. Adverse events.
	NCT01687257: A phase 2, multicenter, open-label, randomized study to investigate the safety and efficacy of GS-7977 and ribavirin administered for 24 weeks in patients infected with chronic HCV with cirrhosis and portal hypertension with or without liver decompensation.	SVR. Adverse events.
	NCT01364090: A phase IV, open-label, multicentre, international trial of response guided treatment with directly observed pegylated interferon alfa 2b and self administered ribavirin for patients with chronic HCV genotype 2 or 3 and ongoing injection drug use	SVR. Adverse events. Quality of life.
Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon.	NCT01581203: A phase 3 study with asunaprevir and daclatasvir (DUAL) for null or partial responders to peginterferon alfa and ribavirin , intolerant or ineligible to P/R subjects and treatment-naive subjects with chronic genotype 1b infection	SVR. Adverse events, including serious adverse events and grade 3-4 laboratory abnormalities.
	NCT01682720: A phase 3, multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of GS-7977 (Sofosbuvir)+ribavirin for 12 weeks in treatment naive and treatment experienced subjects with chronic genotype 2 or 3 HCV infection.	SVR.
	NCT01497366: A phase 3, multicenter, randomized, active-controlled study to investigate the safety and efficacy of PSI-7977 and ribavirin for 12 Weeks compared to pegylated interferon and ribavirin for 24 Weeks in treatment-naïve patients with chronic genotype 2 or 3 HCV infection.	SVR. Adverse events, including serious adverse events and grade 3-4 laboratory abnormalities.
	NCT01497834: A phase 3 Japanese study of BMS-790052 plus BMS-650032 combination therapy in chronic hepatitis C genotype 1b infected subjects who are non response to interferon plus ribavirin and interferon based therapy ineligible naive/intolerant.	SVR. Adverse events, including serious adverse events and grade 3-4 laboratory abnormalities.
Lack of studies in screen detected patients.	No studies identified.	Not applicable.

**Table 13. Selected ongoing studies addressing future research needs (continued)**

Future Research Need	Study Titles	Relevant Planned Outcomes <sup>a</sup>
Lack of studies on effects of using noninvasive methods for assessing liver fibrosis to guide treatment decisions.	No studies identified.	Not applicable.
Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection.	NCT01659567: Prospective observational study on predictors of on-treatment response and sustained virologic response in a cohort of HCV-infected patients treated with pegylated interferons in Georgia	Long-term SVR according to patient characteristics and treatment dose. Adverse events.
	NCT01447446: Non-interventional cohort study on the utilization and impact of dual and triple therapies based on pegylated interferon for the treatment of chronic hepatitis C	Long-term SVR. Treatment according to comorbidities. Adverse events.
	NCT01344889: Global observational cohort study on the prediction of unwanted adverse effects in individuals infected with chronic hepatitis C receiving a long-acting interferon plus ribavirin	Relationship of SVR and patients characteristics to treatment dose and discontinuations. Adverse events .
Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR.	No studies identified.	Not applicable.

Note: HCV= hepatitis C virus, IV=intravenous, SVR=sustained virologic response.

<sup>a</sup> A comprehensive listing of planned outcomes for these studies can be found in Appendix D.

## Proposed Study Designs and Research Questions

The following section discusses overall and specific study design considerations and example research questions for the top-tier future research needs.

### Overall Study Design Considerations

#### Randomized Controlled Trials

*Advantages of randomized controlled trials (RCTs) for producing a valid result.*

Appropriately designed and conducted RCTs are highly suitable for evaluating the benefits and harms of antiviral treatments because they are less susceptible to bias and confounding than observational studies. RCTs are often designed using an efficacy paradigm and are the standard for establishing the efficacy of new drug regimens (research need #3). A shortcoming of such efficacy trials is that while results may be valid, they may be poorly generalizable to real-world situations. However, RCTs can also be designed using an effectiveness paradigm, which would help in addressing several top-tier research needs. For example, RCTs conducted in community-based settings that apply broad eligibility criteria could help address future research needs #1

(studies based on an effectiveness paradigm), #2 (patients with comorbidities). RCTs designed with long-term followup and assessing clinical, rather than virologic outcomes, would help address research need #6 (need to assess long-term outcomes of antiviral regimens). In addition, RCTs could focus on evaluation of patients with HCV identified through screening (research need #4) or the effects of noninvasive methods compared with liver biopsy for selecting patients for antiviral therapy (research need #5).

*Ability to recruit/availability of data.* Comorbidities are common in patients with HCV infection, so this should not be a barrier to recruitment. Also, the possibility of randomization, which can sometimes be a barrier to recruitment, should not be an issue for this research area because RCTs of HCV antiviral treatments always involve the comparison of one antiviral regimen against another; therefore everyone still receives treatment rather than potentially being randomized to placebo. The ability to retain patients in studies could be a barrier to obtaining data on long-term benefits and harms.

*Resource use, size, and duration.* RCTs are typically more resource-intensive than observational studies. In addition, because differences between treatments may be relatively small, adequately powered RCTs may require large sample sizes. Assessment of long-term outcomes, including important clinical outcomes such as mortality, hepatocellular carcinoma, cirrhosis and related complications, and need for transplantation would likely require followup exceeding 3 to 5 years, depending on the sample size.

*Ethical, legal, and social issues.* Those with ongoing intravenous drug use or major psychological or other serious comorbidities have frequently been excluded from RCTs of antiviral therapies and may pose a challenge in terms of patient recruitment or clinician buy-in. As discussed above, the availability of effective antiviral treatments largely precludes the use of placebo controls in RCTs for ethical reasons.

## **Cohort Studies**

*Advantages of cohort studies for producing a valid result.* It is not possible to evaluate the association between achieving and not achieving an SVR following antiviral treatment and clinical outcomes with RCTs because patients cannot be randomized to whether or not they experience an SVR (they can only be randomized to a treatment), therefore cohort studies are useful for this purpose. However, cohort studies are more prone to bias and confounding than RCTs since groups are not randomized. Therefore, it is critical for cohort studies evaluating this association to adequately adjust for the key factors known to be associated with poorer prognosis in patients with HCV infection (such as age, race, baseline fibrosis, viral load, genotype, and others).

Cohort studies could also be used to address long-term clinical outcomes such as mortality, cirrhosis, hepatocellular carcinoma, and need for transplantation (future research need #6), as it is often more feasible to analyze long populations with longer followup using a cohort rather than RCT design.

*Ability to recruit/availability of data.* Large existing registries of patients with HCV infection could be a more efficient source of data than assembling a new cohort, though analysis would necessarily be retrospective. To be most useful, registry data should include clinical information, in addition to information available from administrative databases.

*Resource use, size, and duration.* Given the large sample sizes and long duration of followup needed to evaluate long-term clinical outcomes, cohort studies would likely be more feasible than RCTs as they generally require fewer resources and could be performed retrospectively; however, studies spanning many years could still be costly.

*Ethical, legal, and social issues.* Standard ethical issues in the design and conduct of observational studies include maintenance of data security, and participant privacy and confidentiality.

## Specific Study Design and Research Question Considerations

We provide the research questions as examples, though the nature of the research needs could yield a number of research questions.

### Future Research Need #1: Studies Designed Using Effectiveness Paradigm

The need for studies using an effectiveness paradigm is a general issue relevant across many research questions. RCTs as well as cohort studies that address any of the Key Questions evaluated in the CER would help address this future research need if they are based in community settings, employ broad inclusion criteria, reflect treatment as observed in real-world practice (including lower adherence), evaluate clinical as well as virologic outcomes, and are designed for long-term followup. Example research questions that could address this research need are, “What is the comparative effectiveness of different antiviral regimens in patients recruited from community settings, using broad inclusion criteria?” and “How does the efficacy of antiviral drugs change with lower treatment adherence?”

**Table 14. PICOT specifications for Future Research Need #1**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
What is the comparative effectiveness of different antiviral regimens in patients recruited from community settings, using broad inclusion criteria?	RCT and cohort.	Patients with HCV, recruited from community settings using broad inclusion criteria.	Various antiviral regimens.	One antiviral regimen vs. another.	Clinical (not just intermediate) outcomes.	Long-term followup to adequately evaluate clinical outcomes.
How does efficacy of antiviral drugs change with lower treatment adherence?				Higher vs. lower treatment adherence.		

Note: HCV=hepatitis C virus, PICOT= Population, Intervention, Comparator, Outcome, and Timing, RCT=randomized controlled trial.

### Future Research Need #2: Studies Enrolling Broader Spectrum of Patients, Including Those With Medical and Psychological Comorbidities Seen in Clinical Practice, Such as Advanced Cirrhosis and IV Drug Users

This need is related to future research need #1, but focused on the patient populations enrolled in the studies. As for future research need #1, RCTs and cohort studies that address any of the Key Questions evaluated in the CER that employ broader inclusion criteria would help address this future research need and help guide treatment decisions in patients commonly encountered in clinical practice but typically excluded from efficacy trials. An example research question that could address this research need is, “How do outcomes of antiviral treatments differ in patients with HCV who are IV drug users versus patients without IV drug use?”

**Table 15. PICOT specifications for Future Research Need #2**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
How do outcomes of antiviral treatments differ in patients with HCV who are IV drug users vs. patients without IV drug use?	RCT and cohort.	HCV patients.	Various antiviral regimens.	Antiviral therapy in HCV patients with IV drug use vs. those without IV drug use.	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV=hepatitis C virus, IV=intravenous, PICOT= Population, Intervention, Comparator, Outcome, and Timing, RCT=randomized controlled trial.

**Future Research Need #3: Studies of New Drugs Currently in Clinical Phases of Testing, Including Oral Regimens Without Interferon**

Stakeholders emphasized the expected availability within the next few years of interferon-sparing, all-oral antiviral regimens that will represent a major milestone in HCV treatment. In fact, some patients are opting against treatment at this time with the expectation that such regimens will soon be available. Although the CER focused on current FDA-approved antiviral regimens, any new therapy that is approved would become within scope. The standard study design to evaluate new drug regimens and obtain FDA approval is an RCT using an efficacy design, typically focusing on SVR rates (Key Question 2a in the CER). New regimens will likely be compared against pegylated interferon plus ribavirin, with new trials of genotype 1 infection patients comparing effects of new regimens versus telaprevir or boceprevir plus pegylated interferon plus ribavirin. An example research question that could address this research need is, “What is the comparative effectiveness of oral antiviral regimens without interferon for HCV versus interferon-based regimens?”

**Table 16. PICOT specifications for Future Research Need #3**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
What is the comparative effectiveness of oral antiviral regimens without interferon for HCV versus interferon-based regimens?	RCT	Treatment eligible patients with HCV.	Oral antiviral regimens without interferon.	Interferon-based antiviral therapy.	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV=hepatitis C virus, PICOT= Population, Intervention, Comparator, Outcome, and Timing, RCT=randomized controlled trial.

**Future Research Need #4: Studies of Screen-Detected Patients**

Screen-detected patients may have less severe disease at baseline than patients identified based on symptoms of liver disease or elevated liver function test. Studies that address any of the Key Questions in the CER that evaluate antiviral treatments in HCV-infected patients identified through screening would be helpful for understanding benefits and harms of treatment in this population and would be helpful for informing screening decisions.<sup>34</sup> An example research

question that could address this research need is, “How does the efficacy of antiviral treatment for HCV differ in patients identified through screening versus those identified based on symptoms or abnormal liver tests?”

**Table 17. PICOT specifications for Future Research Need #4**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
How does the efficacy of antiviral treatment for HCV differ in patients identified through screening vs. those identified based on symptoms or abnormal liver tests?	RCT or cohort.	Individuals with HCV.	Antiviral regimens.	Screen-detected vs. symptomatic individuals with HCV or those with elevated liver function tests.	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV=hepatitis C virus, PICOT= Population, Intervention, Comparator, Outcome, and Timing, RCT=randomized controlled trial.

### **Future Research Need #5: Studies Using Noninvasive Methods for Assessing Liver Fibrosis to Guide Treatment Decisions**

Stakeholders emphasized that liver biopsy is no longer performed in all patients who are being considered for antiviral therapy, due to the availability of noninvasive methods for assessing liver fibrosis and more effective treatments. In addition, liver biopsy is associated with a small risk of serious harms (primarily pain and bleeding). However, only one small observational study has evaluated treatment outcomes in patients selected for treatment without a biopsy.<sup>35</sup> This future research need was not directly addressed in the CER. An example research question that could address this research need is, “What is the comparative effectiveness of antiviral treatments in patients selected for therapy based on a liver biopsy versus those selected for treatment without undergoing a liver biopsy?”

**Table 18. PICOT specifications for Future Research Need #5**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
What is the comparative effectiveness of antiviral treatments in patients selected for therapy based on a liver biopsy vs. those selected for treatment without undergoing a liver biopsy?	RCT or cohort.	Patients with HCV.	Antiviral regimens.	Liver biopsy vs. noninvasive methods for assessing for fibrosis prior to initiating antiviral therapy.	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV=hepatitis C virus, PICOT= Population, Intervention, Comparator, Outcome, and Timing, RCT=randomized controlled trial.

## Future Research Need #6: Studies Assessing Important Long-Term Clinical Outcomes

Evaluating the comparative effectiveness of current antiviral regimens on clinical outcomes in randomized trials or cohort studies is a challenge due to the long lead time and large samples necessary to adequately assess these outcomes. This might be more feasible if the studies were to focus on populations at higher risk for complications from chronic HCV infection (e.g., patients with baseline cirrhosis, high viral load, or other risk factors for progression). RCTs and cohort studies that address Key Questions 1a and 1b in the CER would help address this future research need if they are designed to assess long-term outcomes. An important challenge in carrying out such studies is the potential for high attrition over time. An example research question that could address this research need is, “What are the effects of antiviral therapy on clinical outcomes in patients at higher risk for disease progression?”

**Table 19. PICOT specifications for Future Research Need #6**

Example Research Question(s)	Proposed Study Design(s)	P	I	C	O	T
What are the effects of antiviral therapy on clinical outcomes in patients at higher risk for disease progression?	Cohort.	Patients with HCV.	Antiviral therapy.	Antiviral therapy vs. no antiviral, or one antiviral regimen vs. another.	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV=hepatitis C virus, PICOT= Population, Intervention, Comparator, Outcome, and Timing.

## Future Research Need #7: Studies That Adequately Control for Potential Confounders Reporting Clinical Outcomes in Patients Who Experience SVR With Those Who Do Not Experience SVR

## Future Research Need #8: Need for Methodologically Rigorous Studies Conducted in Settings Applicable to U.S. Populations Evaluating the Association Between Achieving an SVR and Improvements in Clinical Outcomes

The CER identified only one study on the association between achieving an SVR and clinical outcomes that controlled well for confounders.<sup>8</sup> Additional large, cohort studies that addressed Key Question 4 from the CER that control for important confounders, including genotype, age, sex, race, viral load, baseline fibrosis, liver function tests, comorbidities, and body weight would help address this future research need. Additionally, many of the studies included in the CER evaluated Asian populations, where the risk of hepatocellular carcinoma and other complications of HCV infection may be higher than in the U.S. Therefore, more well-controlled studies in populations applicable to the U.S. are needed. An example research question that could address these research needs is, “How do outcomes differ among U.S. patients with HCV infection who experience an SVR versus those who do not experience an SVR after antiviral therapy?”

**Table 20. PICOT specifications for Future Research Needs #7 and #8**

<b>Example Research Question(s)</b>	<b>Proposed Study Design(s)</b>	<b>P</b>	<b>I</b>	<b>C</b>	<b>O</b>	<b>T</b>
How do outcomes differ among U.S. patients who experience SVR vs. patients who do not experience an SVR after antiviral therapy?	Cohort studies.	Patients with HCV infection who receive antiviral therapy.	Antiviral therapy.	Patients who experience SVR vs. those who do not experience SVR after antiviral therapy (controlled for important confounders).	Clinical and intermediate outcomes.	Long-term followup.

Note: HCV = hepatitis C virus, PICOT = Population, Intervention, Comparator, Outcome, and Timing, SVR = sustained virologic response, U.S.=United States.

## Discussion

Based on the 2012 CER, and with the input of stakeholders, we identified 12 evidence gaps, seven of which were prioritized as top-tier research needs, and the remainder as second-tier research needs based on the priority rankings of stakeholders. Most of the research gaps did not suggest new research questions to be addressed; rather they primarily identified the need for more applicable and methodologically rigorous studies; therefore the research questions provided are examples. In fact, a number of the research gaps (such as the need for studies that evaluate an effectiveness paradigm, studies that evaluate patients with important comorbidities, and studies that are not funded by the pharmaceutical industry) are relevant across many research questions applicable to understanding the comparative effectiveness of antiviral treatments for HCV.

A limitation of our report is the omission of potentially important research needs due to the requirement of the needs to be within the scope of the original CER. For example, the CER did not evaluate patients with HIV or hepatitis B virus coinfection, or patients who had previously been treated for HCV infection. It also excluded children. Because the CER did not evaluate the state of the evidence for these populations, the extent of research gaps and availability of research was not known. Such areas could be the subject of nominations for future CERs in the EHC program. The precedent for this limitation was initially discussed with the stakeholders during the webinar, which precluded any out of scope gaps from being raised at subsequent opportunities.

Another limitation is that we also had a small sample of stakeholders, with limited representation of some stakeholder perspectives. In addition, standardized and validated methods for selecting stakeholders and synthesize diverse stakeholder viewpoints are not yet available, but would be helpful for Future Research Needs projects.

The rapidly evolving nature of antiviral HCV treatments suggests that even a CER completed this year will need to be updated in the near future. Stakeholders emphasized that all-oral, interferon-sparing regimens are expected within the next few years and will likely have a major impact on clinical practice.

## **Conclusion**

Future research needs as prioritized by a stakeholder group representing diverse perspectives focused on the need for more methodologically rigorous and applicable research to better understand the comparative effectiveness of antiviral treatments for HCV infection in antiviral-naïve patients. Clinical trials of all-oral, interferon-sparing regimens are ongoing and illustrate the rapidly evolving nature of HCV treatments.

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# Acronyms

AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
EHC	Effective Health Care
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
HCV	Hepatitis C virus
PICOT	Population, Intervention, Comparator, Outcome, Timing
RCT	Randomized Controlled Trial
RR	Relative risk
SVR	Sustained virologic response
U.S.	United States

# Appendix A. Initial Prioritization Survey

[SURVEY PREVIEW MODE] Hepatitis C Future Research Needs Questionnaire #1 Survey - Google Chrome  
www.surveymonkey.com/r.aspx?PREVIEW\_MODE=DO\_NOT\_USE\_THIS\_LINK\_FOR\_COLLECTION&sm=%2BF1B8V%2B%2B%2B%2F0d1%2BLA9gGud9B2d3%2B-Cof4r%2BNe%3d

## Hepatitis C Future Research Needs Questionnaire #1

Exit this survey

**\* 1. What is your stakeholder perspective? (Select all that apply.)**

- Clinician
- Researcher
- Research Funder
- Policymaker
- Payer
- Consumer Advocate

**\* 2. Please complete the information below:**

Name:

Degree(s):

Address:

Address 2:

City/Town:

State:

ZIP:

Country:

Email Address:

Phone Number:

**3. What would you, or members of your stakeholder group, most like to know about treatment for Hepatitis C?**

*Gaps discussed on call:*  
**Instructions:**  
Please provide your thoughts on these gaps and whether you think they are of high, medium, or low priority and why. Please feel free to use narrative as much as possible in the space next to each gap to describe the areas of research that you think are most important. You may want to consider the following criteria in your feedback: burden of disease, high public interest, vulnerable populations, utilization of existing resources, potential impact, etc. (Note that ranking in relation to the other gaps will occur in the next questionnaire.)





**11. Area of focus: Intervention**

Lack of studies on effects of using non-invasive methods for assessing liver fibrosis to guide treatment decision

High Priority

Medium Priority

Low Priority

Please provide feedback here:

**12. Area of focus: Comparator**

Lack of head-to-head studies comparing triple therapy regimens (telaprevir or boceprevir + pegylated interferon + ribavirin) with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors

High Priority

Medium Priority

Low Priority

Please provide feedback here:

**13. Area of focus: Comparator**

Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR

High Priority

Medium Priority

Low Priority

Please provide feedback here:

**14. Area of focus: Outcomes/Timing**

Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection

High Priority

Medium Priority

Low Priority





# Appendix B. Final Prioritization Survey

[SURVEY PREVIEW MODE] Hepatitis C Future Research Needs Questionnaire #2 Survey - Google Chrome  
www.surveymonkey.com/s.aspx?PREVIEW\_MODE=DO\_NOT\_USE\_THIS\_LINK\_FOR\_COLLECTION&sm=410162rz2F%2b2GQYbQZXT2016Q5w5nfYb6p7Y9MwPK%3d

## Hepatitis C Future Research Needs Questionnaire #2

Exit this survey

### Ranking

**\* 1. Stakeholder Information:**

**Name:**

Instructions:  
The purpose of Questionnaire #2 is to rank the top future research priorities. A list of the 12 highest ranked topics from Questionnaire #1 is included below. Please reflect on which topics you feel are the highest priority and rank them from 1 to 12, with 1 being the most clinically important. When making your prioritization, keep in mind that we are trying to understand what areas of research have the highest potential to make an immediate impact as well as which research topics you think should be conducted first. Please consider the Effective Health Care's Program Selection Criteria, which includes appropriateness, importance, desirability of new research/duplication, feasibility, and potential impact (described below) when making your prioritization decisions.

For each of the following, please select a rank for each gap, with 1 being highest priority

Effective Health Care Program's Selection Criteria

**Appropriateness:**

- Represents a health care drug, intervention, device, technology or health care system/setting available (or soon to be available) in the United States.
- Relevant to 1013 enrollees (Medicare, Medicaid, S-CHIP), or other federal health care programs.
- Represents one of the priority conditions designated by the United States Department of Health and Human Services.

**Importance:**

- Represents a significant disease burden, large proportion or priority population.
- Is of high public interest; affects health care decision-making, outcomes, or costs for a large proportion of the United States population or for a priority population in particular.
- Was nominated/strongly supported by one or more stakeholder groups.
- Represents important uncertainty for decision makers.
- Incorporates issues around both clinical benefits and potential clinical harms.
- Represents important variation in clinical care, or controversy in what constitutes appropriate clinical care.
- Represent high costs to consumers, patients, health care systems or payers; due to common use, high unit costs, or high associated costs.

**Desirability of New Research/Duplication:**

- 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 the Agency for Healthcare Research and Quality or others).

**Feasibility:**

- Effectively uses existing research and knowledge by considering adequacy of research for conducting a systematic review, and newly available evidence.

**Potential Impact:**

- Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or

[SURVEY PREVIEW MODE] Hepatitis C Future Research Needs Questionnaire #7 Survey - Google Chrome

www.surveymonkey.com/s.aspx?PREVIEW\_MODE=DO\_NOT\_USE\_THIS\_LINK\_FOR\_COLLECTION&sm=410162r2P%2b5Q7bQZIT2016Q5w5mFyBp7r94NeR%3d

\* Potential for significant health impact, significant economic impact, potential for change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups.

**\*2. Please rank the gaps in order of priority, with no overlap (1 = Highest Priority, 12 = Lowest Priority, with no gap receiving the same ranking as another)**

	1 - Highest Priority	2	3	4	5	6	7	8	9	10	11	12 - Lowest Priority
Lack of studies in screen detected patients	<input type="radio"/>											
Lack of studies enrolling broader spectrum of patients, including those with medical and psychological comorbidities seen in clinical practice, such as advanced cirrhosis and IV drug users	<input type="radio"/>											
Lack of studies that adequately control for potential confounders reporting clinical outcomes in patients who experience SVR with those who do not experience SVR	<input type="radio"/>											
Need for well-designed, independently funded studies. Almost all of the randomized trials were funded by pharmaceutical companies. Such studies tend to report more favorable results from drugs produced by the funder than studies funded by governmental or other sources.	<input type="radio"/>											
Lack of studies enrolling patients with advanced age (>65-70 years)	<input type="radio"/>											
Lack of studies reporting long-term followup of patients exposed to telaprevir and bocoprevir to understand the long-term harms associated with use of telaprevir and bocoprevir	<input type="radio"/>											
Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon	<input type="radio"/>											
Need for methodologically rigorous studies conducted in settings applicable to U.S. populations evaluating the association between achieving an SVR and improvements in clinical outcomes	<input type="radio"/>											
Lack of studies evaluating the usefulness of genomics and other methods for individualized treatment decisions in patients with HCV infection using genomics or other methods (e.g., treatment algorithms) and how these treatment decisions affect clinical outcomes	<input type="radio"/>											

[SURVEY PREVIEW MODE] Hepatitis C Future Research Needs Questionnaire #2 Survey - Google Chrome

www.surveymonkey.com/s.aspx?PREVIEW\_MODE=DO\_NOT\_USE\_THIS\_LINK\_FOR\_COLLECTION&sm=410162z2P%2bGQ1bQZt2016Q5svSeFY28p3194NpH%3d

Need for evidence on new drugs currently in clinical phases, including oral regimens without interferon

Need for methodologically rigorous studies conducted in settings applicable to U.S. populations evaluating the association between achieving an SVR and improvements in clinical outcomes

Lack of studies evaluating the usefulness of genomics and other methods for individualized treatment decisions in patients with HCV infection using genomics or other methods (e.g., treatment algorithms) and how these treatment decisions affect clinical outcomes

Need for studies designed using an effectiveness paradigm to understand real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials

Lack of studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection

Lack of studies on effects of using non-invasive methods for assessing liver fibrosis to guide treatment decisions

You have completed questionnaire #2. Thank You.

Done

Powered by **SurveyMonkey**  
Check out our [sample surveys](#) and create your own now!

# **Appendix C. Search Strategy for Ongoing and Recently Completed Studies**

## **Ovid MEDLINE: Search date through August 28, 2012**

**Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or  
hepacivirus\$.mp. or HCV.mp.**

**Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon  
Alpha-2b/ or Interferon\$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or  
IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp.  
or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-  
2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon  
alpha 2b.mp. or pegylated interferon\$.mp. or IFN\$.mp. or PEG IFN\$.mp. or Ribavirin/  
ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor\$.mp. or  
polymerase inhibit\$.mp. or HCV protease\$.mp. or telaprevir.mp. or boceprevir.mp.**

**1 and 2**

**(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or  
clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab.  
or (systematic adj1 review).ti,ab.**

**3 and 4**

**limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64  
years)" or "all aged (65 and over)"))**

**(unsafe or safety or harm\$ or complication\$ or poison\$ or risk\$).mp. or AE.fs. or MO.fs. or  
PO.fs. or TO.fs. or CT.fs. or side-effect\$.mp. or (undesirable adj1 effect\$).mp. or  
(treatment adj1 emergent).mp. or tolerab\$.mp. or toxic\$.mp. or adrs.mp. or (adverse adj2  
(effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.**

**1 and 2 and 7**

**4 and 8**

**limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64  
years)" or "all aged (65 and over)"))**

**Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or  
Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or  
Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/**

**1 and 11**

# **Cochrane Database of Systematic Reviews & Database of Abstracts of Reviews of Effects: Search date through August 28, 2012**

**“Hepatitis C” OR Hepacivirus OR HCV (Title, Abstract, Keyword)**

**Limit to reviews, published 2002-2012**

## **SCOPUS: Search date through August 28, 2012**

**TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)**

**(TITLE-ABS-KEY(“antiviral agent\*” OR interferon\* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon\*” OR ifn\* OR peg ifn\* OR ribavirin OR rbv OR “protease inhibitor\*” OR “polymerase inhibitor\*” OR “hcv protease\*” OR telaprevir))**

**TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly)**

**(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent\*” OR interferon\* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon\*” OR ifn\* OR peg ifn\* OR ribavirin OR rbv OR “protease inhibitor\*” OR “polymerase inhibitor\*” OR “hcv protease\*” OR telapr))) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly))**

**(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent\*” OR interferon\* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon\*” OR ifn\* OR peg ifn\*))**

OR ribavirin OR rbv OR "protease inhibitor\*" OR "polymerase inhibitor\*" OR "hcv protease\*" OR telapr)) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly))

(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent\*" OR interferon\* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon\*" OR ifn\* OR peg ifn\* OR ribavirin OR rbv OR "protease inhibitor\*" OR "polymerase inhibitor\*" OR "hcv protease\*" OR telapr)) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly)) AND (LIMIT-TO(PUBYEAR, 2012) OR (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002))

TITLE-ABS-KEY(unsafe OR safety OR harm\* OR complication\* OR poison\* OR risk\* OR side-effect\* OR "side effect\*" OR "undesirable effect\*" OR "treatment emergent" OR tolerab\* OR toxic\* OR "adverse effect\*" OR "adverse reaction\*" OR "adverse event\*" OR "adverse outcome\*"))

(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent\*" OR interferon\* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon\*" OR ifn\* OR peg ifn\* OR ribavirin OR rbv OR "protease inhibitor\*" OR "polymerase inhibitor\*" OR "hcv protease\*" OR telapr)) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm\* OR complication\* OR poison\* OR risk\* OR side-effect\* OR "side effect\*" OR "undesirable effect\*" OR "treatment emergent" OR tolerab\* OR toxic\* OR "adverse effect\*" OR "adverse reaction\*" OR "adverse event\*" OR "adverse outcome\*"))

(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent\*" OR interferon\* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon\*" OR ifn\* OR peg ifn\*

OR ribavirin OR rbv OR "protease inhibitor\*" OR "polymerase inhibitor\*" OR "hcv protease\*" OR telapr)) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm\* OR complication\* OR poison\* OR risk\* OR side-effect\* OR "side effect\*" OR "undesirable effect\*" OR "treatment emergent" OR tolerab\* OR toxic\* OR "adverse effect\*" OR "adverse reaction\*" OR "adverse event\*" OR "adverse outcome\*")) AND (LIMIT-TO (LIMIT-TO(PUBYEAR, 2012) OR (PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003))

TITLE-ABS-KEY(counseling OR "health education" OR "patient education" OR psychotherapy OR "behavior therapy" OR "cognitive therapy" OR immuniz\* OR immunotherapy OR "socioenvironmental therapy" OR "cognitive behavior\* therapy" OR vaccine\*)

(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND (TITLE-ABS-KEY(cohort\* OR "meta analysis" OR "randomized controlled trial\*" OR "systematic review\*" OR "controlled clinical trial\*" OR "placebo" OR "clinical trial\*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(counseling OR "health education" OR "patient education" OR psychotherapy OR "behavior therapy" OR "cognitive therapy" OR immuniz\* OR immunotherapy OR "socioenvironmental therapy" OR "cognitive behavior\* therapy" OR vaccine\*))

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hepatitis/ or (Hepatitis C or hepacivirus\$ or HCV).mp.

[exp treatment/ or exp intervention/ or exp psychotherapy/ or exp alcohol rehabilitation/ or exp counseling/ or exp support groups/ or exp rehabilitation/ or exp mental health services/ or exp community services/ or exp outreach programs/ or exp drug rehabilitation/ or exp sobriety/ or exp detoxification/ or exp drug rehabilitation/ or exp treatment outcomes/ or exp alcoholics anonymous/]

alcohol\*.mp.

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## Appendix D. Ongoing Clinical Trials of Interventions for Hepatitis C Infection

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT00485342	Multicentric, Controlled and Randomised Open Clinical Trial Investigating the Efficacy and Safety of Dose Adaptation of Ribavirin Using Pharmacologic Measures of Ribavirin Exposition During Combination Peginterferon Alfa-2 and Ribavirin Treatment in Naive Patients With Chronic Hepatitis C of Genotype 1 on a First Combination Therapy.	Pegylated interferon alfa-2a and ribavirin  Ribavirin with adaptation dose	Adult	Inter group comparison of SVR rates as defined by the proportion of subjects with a negative PCR HCV RNA test at Week 72  Efficacy endpoints  Safety endpoints  Economic endpoints
NCT00491244	Pegylated Interferon Alfa-2a Plus Low Dose Ribavirin Versus Pegylated Interferon Alfa-2a Alone for Treatment-naïve Dialysis Patients With Chronic Hepatitis C.	Pegylated interferon alfa-2a  Low-dose ribavirin	Adult	SVR  Drop-out rate  Histologic response  Biochemical response
NCT00540345	Four Arms, Multicenter, Open Label Study of Tailored Regimens With Peginterferon Plus Ribavirin for Genotype 2 Chronic Hepatitis C.	Pegylated interferon alfa-2a  Ribavirin	Adult  Senior	Efficacy - rapid virologic response, HCV RNA seronegative by PCR at week 4 SVR, HCV RNA seronegative by PCR throughout 24-week off-treatment period  Safety - adverse event rate and profile

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT00780416	A Phase 3 Study of MP-424 in Combination With Peginterferon Alfa-2b and Ribavirin, in Treatment-Naïve Subjects With Genotype 1 Hepatitis C.	MP-424 Pegylated interferon alfa-2b Ribavirin	Adult	The percentage of subjects achieving undetectable HCV RNA at 24 weeks after treatment completion (SVR)
NCT01197157	Impact of Nitazoxanide on Virologic Responses in Chronic HCV Infected Patients With Genotype 4: A Placebo-controlled Randomized Trial.	Placebo Nitazoxanide	Adult	Assessment of efficacy of nitazoxanide as an add-on therapy in terms of achieving a SVR  Assessment of rapid virologic response  Assessment of early virologic response  Assessment of end-of-treatment response  Safety of nitazoxanide  Assessment of the efficacy of nitazoxanide monotherapy following the lead-in phase
NCT01241760	A Randomized, Open-label, Phase 3 Study of Telaprevir Administered Twice Daily or Every 8 Hours in Combination With Pegylated Interferon Alfa-2a and Ribavirin in Treatment-naïve Subjects With Genotype 1 Chronic Hepatitis C Virus Infection.	Ribavirin Telaprevir Pegylated interferon alfa-2a	Adult Senior	Proportion of patients achieving undetectable plasma HCV RNA levels  Safety and tolerability of the two dose regimens of telaprevir  Effect of IL28B genotype on viral response  Pharmacokinetics of telaprevir, pegylated interferonalpha-2a, and Ribavirin and pharmacokinetic-pharmacodynamic relationships for safety and efficacy  Changes from baseline in the amino acid sequence of the HCV non-structural 3-4A region

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01263860	A Randomized Trial of 24-Week Versus 48-Week Courses of Peginterferon Plus.	Pegylated interferon alfa-2a Ribavirin Pegylated interferon alfa-2a Ribavirin	Adult Senior	SVR Change in health related quality as measured by Short Form 36 from baseline to 24 weeks after treatment completion Sick leave in patients treated for 24 or 48 weeks treatment
NCT01276756	Randomized Study for the Assessment of Nitazoxanide in the Treatment of Chronic Hepatitis C Genotype 4.	Pegylated interferon alfa-2a Ribavirin Nitazoxanide	Adult	SVR Rapid virologic response Early virologic response End-of-treatment response Safety of nitazoxanide (occurrence of adverse events)
NCT01289782	A Phase III, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a and Ribavirin in Treatment-naive, Genotype 1 Hepatitis C-infected Subjects.	TMC435 Pegylated interferon alfa-2a Ribavirin Placebo	Adult Senior	Proportion of patients with a SVR 24 weeks after treatment completion

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01289782	A Phase III, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-infected Subjects.	TMC435 Pegylated interferon alfa-2a Ribavirin Placebo	Adult Senior	SVR
NCT01290679	Phase III, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, and Tolerability of TMC435 vs Placebo as Part of a Treatment Regimen Including Peginterferon a-2a and Ribavirin or Peginterferon a-2b and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-infected Subjects.	TMC435 Pegylated interferon alfa-2a Pegylated interferon alfa-2b Ribavirin Placebo	Adult Senior	SVR

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01292239	A Phase III, Randomized, Double-blind, Placebo-controlled Trial in Japan to Investigate the Efficacy and Safety of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon Alfa-2a and Ribavirin in Treatment-Naive, Genotype 1, Hepatitis C-infected Subjects.	Placebo TMC435	Adult Senior	Proportion of patients with SVR 24 weeks after treatment completion  Proportion of patients with SVR 12 weeks after treatment completion  Proportion of patients with 2 log 10 IU/mL or more decrease in HCV RNA  Proportion of patients with undetectable HCV RNA  Proportion of patients with viral breakthrough  Proportion of patients showing viral relapse  Number of patients with adverse events  Plasma concentrations of TMC435

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01297270	A Phase III, Randomized, Double Blind and Placebo Controlled Study of Once Daily BI 201335 120 mg for 24 Weeks and BI 201335 240 mg for 12 Weeks in Combination With Pegylated Interferon Alpha and Ribavirin in Treatment Naive Patients With Genotype 1 Chronic Hepatitis C Infection.	BI201335 Pegylated interferon alfa Ribavirin	Adult Senior	SVR: Plasma HCV RNA level <25 IU/mL, undetected 24 weeks after treatment completion  Occurrence of adverse events (overall, and classified into mild/moderate/severe)  Occurrence of adverse events leading to treatment discontinuation  Occurrence of serious adverse events  Occurrence of drug-related adverse events as assessed by the investigator  Occurrence of laboratory test abnormalities  Central tendency and changes from baseline in laboratory test values over time  SVR: Plasma HCV RNA level < 25 IU/mL, undetected 12 weeks after treatment completion  Early treatment success: - Plasma HCV RNA level < 25 IU/mL (detected or undetected) at week 4 and HCV RNA < 25 IU/mL, undetected at week 8  Alanine aminotransferase normalization: in normal range 24 weeks after treatment completion

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01318694	A Randomized, Double-blind, Placebo-controlled Trial of the Efficacy and Safety of DEB025/Alisporivir in Combination With Peg-IFN $\alpha$ 2a and Ribavirin in Hepatitis C Genotype 1 Treatment-naïve.	<p>Standard of care (Pegylated interferon alfa-2a once weekly + Ribavirin twice daily) + DEB025</p> <p>Standard of care + DEB025 400 mg</p> <p>Standard of care + DEB025</p> <p>Standard of care + Placebo for 48 weeks</p>	<p>Adult</p> <p>Senior</p>	<p>SVR, , defined as serum HCV RNA below limit of quantification 12 weeks after treatment completion</p> <p>SVR week 24 - -duration of DEB025+Ribavirin+ pegylated interferon alfa-2a therapy followed by Ribavirin+pegylated interferon alfa-2a therapy for up to 48 weeks needed to achieve SVR 12 weeks after treatment completion</p> <p>Rapid virologic response by limit of detection, rapid virologic response by limit of quantification, - defined as serum HCV RNA below limit of detection or limit of quantification respectively after 4 weeks of treatment</p> <p>Treatment response at 12 weeks - defined as HCV RNA undetectable by limit of detection</p> <p>End of treatment response - defined as HCV RNA undetectable by limit of detection, SVR 48 weeks after treatment completion</p> <p>Change in liver enzyme (alainine aminotransferase and bilirubin) and hematological patient profiles (platelets, neutrophils, hemoglobin) during treatment phase</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01323244	A Phase III, Open-Label, Single Arm, Rollover Trial of TMC435 in Combination With Peginterferon Alpha-2A and Ribavirin for HCV Genotype-1 Infected Subjects Who Participated in the Placebo Group of a Phase II/III TMC435 Study, or Who Received DAA Treatment in a Tibotec-Sponsored Phase I Study.	TMC435 Pegylated interferon alfa-2a Ribavirin	Adult Senior	Proportion of participants with SVR Proportion of participants with SVR Number of participants with HCV RNA level >1000 IU/mL Number of participants with viral breakthrough Number of participants with viral relapse Number of participants with normalized alanine aminotransferase levels Number of participants with on-treatment failure Number of participants affected by an adverse event
NCT01343888	A Phase III, Randomised, Double-blind and Placebo-controlled Study of Once Daily BI 201335 120 mg for 12 or 24 Weeks or BI 201335 240 mg for 12 Weeks in Combination With Pegylated interferon-a and Ribavirin in Treatment-naïve Patients With Genotype 1 Chronic Hepatitis C Infection.	Pegylated interferon alfa-2a Ribavirin BI 201335	Adult Senior	SVR after 12 weeks of treatment completion: Plasma HCV RNA level < 25 IU/mL, undetected SVR after 24 weeks of treatment completion: Plasma HCV RNA level < 25 IU/mL, undetected Early treatment success: Plasma HCV RNA level < 25 IU/mL (detected or undetected) at week 4 and HCV RNA < 25 IU/mL undetected at week 8 Alanine aminotransferase and aspartate aminotransferase normalization: in normal range at end of treatment and post-treatment

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01344889	Global Observational Cohort Study on the Prediction of Unwanted Adverse Effects in Individuals Infected With Chronic Hepatitis C Receiving a Long Acting Interferon Plus Ribavirin.	Long-acting interferons  Ribavirin	Adult  Senior	<p>Correlation between baseline patient characteristics and safety related dose reductions/treatment discontinuations of the long-acting interferon or Ribavirin</p> <p>Correlation between safety related dose reductions/treatment discontinuations and SVR, defined as HCV RNA &lt;50 IU/mL at 24 weeks after treatment completion</p> <p>Correlation of on-treatment factors and dose reduction/treatment discontinuation</p> <p>Correlation between degree of dose reductions/treatment interruptions (percentage of actual exposure/treatment administrations in relation to target exposure) and SVR</p> <p>Comparison of on-treatment virological response (rapid virological response, early virological response) in treatment-naive and treatment experienced patients</p> <p>Incidence of adverse events</p>
NCT01364090	A Phase IV, Open-label, Multicentre, International Trial of Response Guided Treatment With Directly Observed Pegylated Interferon Alfa 2b and Self Administered Ribavirin for Patients With Chronic HCV Genotype 2 or 3 and Ongoing Injection Drug Use.	Pegylated interferon alfa-2b  Ribavirin	Adult  Senior	<p>Treatment efficacy</p> <p>Safety and tolerability</p> <p>Treatment adherence</p> <p>Treatment response, (end of treatment and SVR 12 weeks after treatment completion)</p> <p>Behavioral and quality of Life</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01366638	A Phase III, Open-Label Study in Japan to Assess the Efficacy and Safety of TMC435 as Part of a Treatment Regimen Including Peginterferon Alfa-2b and Ribavirin in Hepatitis C, Genotype 1 Infected Subjects.	<p>TMC435</p> <p>Pegylated interferon alfa-2b</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Proportion of patients with SVR 12 and 24 weeks after treatment completion</p> <p>Number of patients with adverse events</p> <p>Plasma concentrations of TMC435</p> <p>Proportion of patients with undetectable HCV RNA</p> <p>Proportion of patients with viral breakthrough</p> <p>Proportion of patients showing viral relapse</p> <p>Proportion of patients within the normal limit of alanine aminotransferase levels</p> <p>Proportion of patients with 2 log 10 IU/mL or more decrease in HCV RNA</p>
NCT01370642	A Phase III Randomized, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Efficacy of MK-7009 When Administered Concomitantly With Peginterferon Alfa-2b and Ribavirin in Japanese Treatment-Naïve Patients With Chronic Hepatitis C Infection.	<p>Vaniprevir</p> <p>Placebo</p> <p>Pegylated interferon alfa-2b</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Proportion of patients achieving SVR</p> <p>Proportion of patients achieving SVR 12 weeks after treatment completion</p> <p>Proportion of participants achieving rapid virologic response</p> <p>Proportion of participants achieving complete early virologic response</p> <p>Proportion of participants achieving undetectable HCV RNA at the end of treatment</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01389323	Open-Label, Single Arm Evaluation of BMS-790052 in Combination With Peg-Interferon Alfa-2a and Ribavirin in Black-African Americans, Latinos and White-Caucasians With Chronic Hepatitis C Genotype 1 Infection.	<p>BMS-790052 (NS5A Replication Complex Inhibitor)</p> <p>Pegylated interferon alfa 2a</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Proportion of subjects with SVR 12 weeks after treatment completion, defined as HCV RNA &lt; limit of quantification (detectable or undetectable) for each cohort</p> <p>Frequency of serious adverse events and discontinuations due to adverse events for each cohort and overall</p> <p>Proportion of subjects with CC, CT, or TT genotype at the IL28B rs12979860 single nucleotide polymorphism who achieves SVR 12 weeks after treatment completion</p> <p>Proportion of subjects who achieve HCV RNA &lt; limit of quantification</p> <p>Proportion of subjects who achieve HCV RNA undetectable</p>
NCT01405027	Boceprevir in Community Practice: Assessing Safety, Efficacy, Compliance and Quality of Life, Impact of an Education Program.	<p>Educational Intervention</p> <p>No Intervention</p>	<p>Adult</p> <p>Senior</p>	<p>Treatment duration compliance rate</p> <p>Dose exposure</p> <p>SVR defined as undetectable plasma HCV RNA at followup week 24</p> <p>Quality of life</p> <p>Number of participants with adverse events</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01446250	A Randomized, Open Label Trial of the Safety and Efficacy of DEB025/Alisporivir in Combination With Pegylated Interferon-α2a and Ribavirin (Peg-INFα2a/RBV) and Boceprevir in Combination With Peg-INFα2a/RBV in African American Treatment-naïve Patients With Chronic Hepatitis C Genotype 1.	<p>DEB025 plus pegylated interferon alfa-2a and Ribavirin fixed duration treatment</p> <p>DEB025 plus pegylated interferon alfa-2a and Ribavirin response guided treatment duration</p> <p>Boceprevir plus pegylated interferon alfa-2a and Ribavirin per label response guided treatment</p>	Adult Senior	<p>Proportion of patients that discontinue study drug or require dose reduction or dose interruption due to treatment-emergent adverse events</p> <p>Proportion of patients with emergence of resistant mutations in each treatment arm</p> <p>Proportion of patients that achieve SVR, defined as serum HCV RNA undetectable by limit of detection 24 weeks after treatment completion</p>
NCT01447420	Clinical Study to Compare Sustained Virological Response in Function of Expression Profile of IL28-b in naïve Patients With Chronic Infection by HCV Genotype 1, With Hepatitis C, Receiving Pegasys and Ribavirin.	<p>Pegylated interferon alfa-2a</p> <p>Ribavirin</p>	Adult Senior	<p>Rate of SVR (undetectable HCV RNA 24 weeks after treatment completion) in relation to Interleukin 28B (IL28-b) expression</p> <p>Incidence of anemia</p> <p>Response rate (rapid/early/end of treatment) in relation to IL28-b expression</p> <p>Correlation between SVR and anemia (hemoglobin levels) during the first month of treatment</p> <p>Correlation between SVR and anemia (hemoglobin levels) after the first month of treatment</p> <p>Correlation between viral load (HCV RNA levels) 12 weeks after treatment completion and SVR</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01448044	A Phase 3 Evaluation of BMS-790052 in Combination With Peg-Interferon Alfa-2a and Ribavirin in Treatment Naive Subjects With Chronic Hepatitis C Genotype 4.	<p>BMS-790052 (NS5A Replication Complex Inhibitor)</p> <p>Placebo matching BMS-790052</p> <p>Pegylated interferon alfa-2a</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Compare rates of SVR 12 weeks after treatment completion for HCV genotype 4 subjects treated with either BMS-790052 or placebo in combination with pegylated interferon ± alfa2a/Ribavirin</p> <p>Proportion of subjects who achieve HCV RNA &lt; limit of quantification</p> <p>Proportion of subjects who achieve HCV RNA undetectable</p> <p>Frequency of serious adverse events and discontinuations due to adverse events for each cohort on treatment</p> <p>Proportion of subjects with SVR 12 or 24 weeks after treatment completion by rs12979860 single nucleotide polymorphism in the IL28B gene</p>
NCT01457937	Boceprevir/Peginterferon Alfa (PegIFN α)-2b/Ribavirin (Riba) in Difficult-to-Treat Menopausal Women With Chronic Hepatitis C Genotype 1 (Gt 1), Either Deemed Nonresponders to Peginterferon/Ribavirin or Treatment-naives (MEN_BOC).	<p>Pegylated interferon alfa</p> <p>Ribavirin</p> <p>Boceprevir</p>	<p>Child</p> <p>Adult</p> <p>Senior</p>	<p>Improvement of SVR in previous treatment failure or naive HCV-positive menopausal women</p> <p>Early virologic response</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01459913	A Phase 3b Study of 2 Treatment Durations of Telaprevir, Peg-IFN (Pegasys®), and Ribavirin (Copegus®) in Treatment-Naïve and Prior Relapser Subjects With Genotype 1 Chronic Hepatitis C and IL28B CC Genotype.	Telaprevir Pegylated interferon alfa-2a  Ribavirin	Adult  Senior	<p>Proportion of subjects assigned to the 12-week regimen of telaprevir, pegylated interferon, and Ribavirin who have SVR 12 weeks after treatment completion</p> <p>Proportion of subjects who have SVR 24 weeks after treatment completion</p> <p>Proportion of subjects who have SVR at week 72</p> <p>Proportion of subjects who have relapse overall and by treatment completion status</p> <p>Proportion of subjects who have on-treatment virologic failure</p> <p>Safety as indicated by adverse events, clinical laboratory results, electrocardiograms, and vital signs</p> <p>Amino acid sequence of the HCV non-structural 3-4A protease domain</p>
NCT01483742	A Study to Evaluate Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Ritonavir-Boosted DANOPREVIR and RO5024048 in Different Combinations in Null Responder or Treatment Naïve Patients With Chronic Hepatitis C and Compensated Cirrhosis.	Danoprevir  Ritonavir Pegylated interferon alfa-2a  Ribavirin	Adult	<p>Incidence of adverse events</p> <p>Area under the concentration-time curve</p> <p>HCV RNA levels assessed by Roche COBAS Taqman HCV test</p> <p>Emergence of viral resistance</p> <p>Virologic response</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01492426	A Phase 3 Evaluation of BMS-790052 (Daclatasvir) Compared With Telaprevir in Combination With Peginterferon Alfa-2a and Ribavirin in Treatment-Naive Patients With Chronic Hepatitis C.	<p>BMS-790052 (Daclatasvir) Telaprevir</p> <p>Pegylated interferon alfa-2a</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Proportion of genotype 1b patients with SVR, defined as HCV RNA &lt; limit of quantification at followup week 12 in each group</p> <p>Proportion of genotype 1b patients with hemoglobin value &lt; 10 g/dL</p> <p>Proportion of genotype 1b patients with rash events</p> <p>Proportion of genotype 1b patients with HCV RNA undetectable at week 12</p> <p>Proportion of genotype 1b patients with HCV RNA undetectable at week 4</p> <p>Proportion of genotype 1b patients with HCV RNA undetectable at Wweeks 4 and 12</p> <p>Proportion of genotype 1b patients with SVR, defined as HCV RNA &lt; limit of quantification at followup week 24 for each cohort</p> <p>Proportion of genotype 1b patients with SVR at followup week 12 based on IL28B rs12979860 single nucleotide polymorphism genotype (CC or non-CC)</p> <p>Proportion of genotype 1a patients with SVR, defined as HCV RNA &lt; limit of quantification at followup week 12 for each cohort</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01497366	A Phase 3, Multicenter, Randomized, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 Weeks Compared to Pegylated Interferon and Ribavirin for 24 Weeks in Treatment-Naïve Patients With Chronic Genotype 2 or 3 HCV Infection.	PSI-7977 in combination with ribavirin  Pegylated interferon in combination with ribavirin	Adult  Senior	Efficacy 12 weeks after treatment completion  Description of Safety with PSI-7977 and Ribavirin  SVR 24 weeks after treatment completion  Amount of circulating HCV RNA  Alaine aminotransferase normalization  Number of subjects with virologic failure  Characterization of drug resistance
NCT01497834	A Phase 3 Japanese Study of BMS-790052 Plus BMS-650032 Combination Therapy in Chronic Hepatitis C Genotype 1b Infected Subjects Who Are Non Response to Interferon Plus Ribavirin and Interferon Based Therapy Ineligible Naive/Intolerant.	BMS-790052 (Daclatasvir)  BMS-650032 (Asunaprevir)	Adult  Senior	Antiviral activity, as determined by the proportion of subjects with SVR 24 weeks after treatment completion  Antiviral activity, as determined by the proportion of subjects who achieve HCV RNA < limit of quantification  Antiviral activity, as determined by the proportion of subjects who achieve undetectable HCV RNA  Safety, as measured by the frequency of severe adverse events, discontinuations due to adverse events, adverse effects by intensity and laboratory abnormalities by toxicity grade  Proportion of subjects with SVR 24 weeks after treatment by IL28B status (CC, CT, or TT genotype at the IL28B rs12979860 single nucleotide polymorphisms)

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01498068	Open-Label, Bridging Study to Determine Efficacy and Safety of Telaprevir, Pegylated-Interferon-alfa-2a and Ribavirin in Treatment-Naïve and Treatment-Experienced Russian Subjects With Genotype 1 Chronic Hepatitis C.	Telaprevir Pegylated interferon alfa-2a Ribavirin	Adult Senior	Proportion of patients having undetectable plasma HCV RNA levels
NCT01508286	Multicenter, Open-label, Early Access Program of Telaprevir in Combination With Peginterferon Alfa and Ribavirin in Genotype 1 Chronic Hepatitis C Subjects With Severe Fibrosis and Compensated Cirrhosis.	Telaprevir Pegylated interferon alfa Ribavirin	Adult Senior	Not reported

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01516918	A Multicenter, Open-Label Phase 2b Pilot Study to Evaluate the Efficacy and Safety of Quadruple Therapy (VX-222, Telaprevir, Peginterferon-Alfa-2, and Ribavirin) in Subjects With Genotype 1 Chronic Hepatitis C With Compensated Cirrhosis.	<p>VX-222</p> <p>Telaprevir</p> <p>Ribavirin</p> <p>Pegylated interferon alfa-2a</p>	<p>Adult</p> <p>Senior</p>	<p>SVR 12 weeks after treatment completion</p> <p>Safety and tolerability as assessed by adverse events, vital signs, 12-lead electrocardiograms and laboratory assessments</p> <p>Proportion of subjects who have an SVR 24 weeks after treatment completion</p> <p>Proportion of subjects who achieve undetectable HCV RNA at weeks 2, 4, 8, and 12 after the first dose of study drug, and at treatment completion</p> <p>Proportion of subjects who have on-treatment virologic failure defined as subjects who either meet a futility rule or who complete the assigned treatment duration and have HCV RNA at treatment completion</p> <p>Association of the IL-28B genotype with SVR after 12 weeks of treatment</p> <p>Amino acid sequence of the nonstructural )3 and 5B proteins in subjects who have treatment failure</p> <p>VX-222, telaprevir, and Ribavirin plasma concentrations and pegylated interferon serum concentrations</p>
NCT01544920	A Phase 3, Safety and Efficacy Study of Boceprevir/Peginterferon Alfa-2a/Ribavirin in Chronic HCV Genotype 1 IL28B CC Subjects.	<p>Pegylated interferon alfa-2a</p> <p>Ribavirin</p> <p>Boceprevir</p>	<p>Adult</p> <p>Senior</p>	<p>Overall number of participants achieving SVR at followup week 24</p> <p>Number of participants achieving SVR at followup week 24 among those participants who had achieved rapid virologic response</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01544920	A Phase 3, Safety and Efficacy Study of Boceprevir/Peginterferon Alfa-2a/Ribavirin in Chronic HCV Genotype 1 IL28B CC Subjects.	Pegylated interferon alfa-2a  Ribavirin  Boceprevir	Adult  Senior	Overall number of participants achieving SVR at followup week 24  Number of participants achieving SVR at followup week 24 among those participants who had achieved rapid virologic response
NCT01567735	An Open-Label, Single-Arm Phase III Study to Evaluate the Efficacy, Safety and Tolerability of TMC435 in Combination With PegIFN Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment-Naïve or Treatment-Experienced, Chronic Hepatitis C Virus Genotype-4 Infected Subjects.	Drug TMC435	Adult  Senior	Proportion of participants achieving SVR 12 weeks after treatment completion  Efficacy of TMC435 with respect to proportion of participants achieving SVR 24 weeks after treatment completion  On-treatment virologic response  On-treatment virologic failure  Evaluation of the viral breakthrough rate  Evaluation of viral relapse rate  Evaluation the safety and tolerability
NCT01579474	Safety, Efficacy and Pharmacokinetics of BI 201335 NA in Patient With Genotype 1 Chronic Hepatitis C Virus Infection in Combination With Pegylated Interferon Alfa-2b and Ribavirin - Cohort 1 for Treatment-naïve Patients: Randomised, Double-blind Part of BI 201335 NA for 12 or 24 Weeks - Cohort 2 for Treatment-experienced Patients: Open-label Part of BI 201335 NA for 24 Weeks.	BI 201335 high dose  BI201335 low dose  Pegylated interferon alfa-2b  Ribavirin	Adult  Senior	SVR, defined as plasma HCV RNV undetectable at 24 weeks after treatment completion  SVR, defined as plasma HCV RNA undetectable at 12 weeks after treatment completion  Early treatment success, defined as plasma HCV RNA <25 IU/mL at week 4 and HCV RNA undetectable at week 8  Alanine aminotransferase normalization, defined as normal at 24 weeks after treatment completion

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01581203	A Phase 3 Study With Asunaprevir and Daclatasvir (DUAL) for Null or Partial Responders to Peginterferon Alfa and Ribavirin (P/R), Intolerant or Ineligible to P/R Subjects and Treatment-Naive Subjects With Chronic Hepatitis C Genotype 1b Infection.	<p>Asunaprevir Daclatasvir</p> <p>Placebo matching Asunaprevir</p> <p>Placebo matching Daclatasvir</p> <p>Pegylated interferon alfa-2a</p> <p>Ribavirin</p>	<p>Adult</p> <p>Senior</p>	<p>Proportion of treated subjects with SVR, defined as HCV RNA &lt; limit of quantification at 12 weeks after treatment completion, for all subjects who are prior null or partial responders to pegylated interferon alfa-2a and Ribavirin or are treatment-naïve</p> <p>Proportion of treated subjects with SVR, defined as HCV RNA &lt; limit of quantification 12 weeks after treatment completion, for subjects who are intolerant or ineligible to pegylated interferon alfa-2a and Ribavirin</p> <p>On treatment safety, as measured by frequency of serious adverse events and discontinuations due to adverse events</p> <p>Differences in rates of selected grade 3-4 laboratory abnormalities during the first 12 weeks between treatments (Asunaprevir + Daclatasvir vs. placebo) for naive subjects</p> <p>Proportion of genotype 1b subjects with SVR (defined as HCV RNA &lt; limit of quantification at 12 weeks after treatment completion) by the rs12979860 single nucleotide polymorphisms in the IL28B gene for each cohort</p> <p>Proportion of genotype 1b subjects with HCV RNA undetectable</p> <p>Proportion of genotypes 1b subjects with HCV RNA &lt; limit of quantification</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01591460	An International, Multicenter, Open-Label Study Evaluating Sustained Virological Response and Safety With Boceprevir in Triple Combination Therapy With Peginterferon Alfa-2a (40KD) and Ribavirin in Treatment-Naïve Patients With Genotype 1 Chronic Hepatitis C.	Boceprevir Pegylated interferon alfa-2a (Pegasys) Ribavirin (Copegus)	Adult Senior	SVR 12 weeks after treatment completion SVR 24 weeks after treatment completion Level of HCV RNA End of treatment response Virologic relapse rate Safety: incidence of adverse events

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01598090	<p>A Phase 3 Blinded Randomized Study of Peginterferon Lambda-1a and Ribavirin Compared to Peginterferon Alfa-2a and Ribavirin, Each Administered With Telaprevir in Subjects With Genotype-1 Chronic Hepatitis C Who Are Treatment-naive or Relapsed on Prior Treatment With Peginterferon Alfa-2a and Ribavirin.</p>	<p>Peginterferon lambda-1a  Pegylated interferon alfa-2a    Ribavirin    Telaprevir</p>	<p>Adult    Senior</p>	<p>Proportion of subjects achieving efficacy as measured by extended rapid virologic response</p> <p>Safety as measured by the frequency of deaths, serious adverse events, drug related adverse events, dose reductions and discontinuations due to adverse events</p> <p>Proportion of subjects achieving efficacy as measured by SVR 12 weeks after treatment completion, defined as HCV RNA &lt; 25 IU/ml</p> <p>Proportion of subjects who achieve efficacy as measured by SVR 12 weeks after treatment completion, defined as HCV RNA &lt; 25 IU/ml</p> <p>Proportion of subjects who achieve efficacy as measured by SVR 24 weeks after treatment completion, defined as HCV RNA &lt; 25 IU/ml</p> <p>Proportion of subjects who achieve efficacy as measured by SVR 12 weeks after treatment completion, defined as HCV RNA &lt; 25 IU/ml in treatment-naive subjects</p> <p>Proportion of subjects who achieve efficacy as measured by extended rapid virologic response, defined as HCV RNA undetectable</p> <p>Proportion of subjects who achieve efficacy as measured by SVR 24 weeks after treatment completion, defined as HCV RNA &lt; 25 IU/ml</p> <p>Number of incidence for Cytopenic abnormalities (anemia is defined by hemoglobin &lt; 10 g/dL, neutropenia as defined by absolute neutrophil count &lt; 750 mm<sup>3</sup>, thrombocytopenia as defined by platelets &lt; 50,000 mm<sup>3</sup>)</p> <p>Number of incidence for flu-like symptoms (as defined by pyrexia or chills or pain)</p> <p>Number of incidence for musculoskeletal symptoms (as defined by arthralgia or myalgia or back pain)</p>

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01608737	A Phase III, Randomised, Double-blind and Placebo-controlled Study of Once Daily BI 201335 for 12 or 24 Weeks in Combination With Pegylated interferon-a and Ribavirin in Treatment-naive and Prior Relapser Patients With Genotype 1 Chronic Hepatitis C Infection.	Pegylated interferon alfa-2a  Ribavirin  Drug BI 201335	Adult  Senior	SVR 12 weeks after treatment completion: Plasma HCV RNA <25 IU/mL undetected  Virologic response\ 24 weeks after treatment completion: Plasma HCV RNA level <25 IU/mL, undetected  Early treatment success: Plasma HCV RNA level <25 IU/mL (detected or undetected) at week 4 and HCV RNA <25 IU/mL, undetected at week 8  Alanine Aminotransferase and Aspartate Aminotransferase normalization: normal at end of treatment and treatment completion
NCT01609049	Open-label, Multicenter, Non-comparative, Prospective Observational Study to Evaluate Efficacy and Safety of Combined Ribavirin and Peginterferon Alfa-2a (40 kDa) Therapy in Patients With Chronic Hepatitis C (CHC) and Compensated Liver Cirrhosis in Real Clinical Practice.	Pegylated interferon alfa-2a  Ribavirin	Adult  Senior	Percentage of patients with undetectable HCV RNA 24 weeks after treatment completion  Percentage of patients with SVR and negative HCV RNA at week 4 and 12 (naive patients)  Percentage of patients with SVR and negative HCV RNA at week 12 (previously treated patients)  Percentage of patients with SVR and decrease in HCV RNA by $\geq \log 10$ from baseline (previously treated and naive patients)  Percentage of patients with SVR who had dose reduction of any drug (Ribavirin or Pegylated interferon alfa-2a) due to adverse events  Incidence of adverse events

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01616524	A Phase 3, Randomized, Double-Blind, Controlled Study Evaluating the Efficacy and Safety of Peginterferon Lambda-1a, With and Without Daclatasvir, Compared to Peginterferon Alfa-2a, Each in Combination With Ribavirin, in the Treatment of Naïve Genotype 2 and 3 Chronic Hepatitis C Subjects.	Pegylated interferon lambda Pegylated interferon alfa-2a Ribavirin Daclatasvir Placebo	Adult Senior	Proportion of subjects who achieve SVR 12 weeks after treatment completion Proportion of subjects with rapid virologic response, undetectable HCVRNA Proportion of subjects with treatment emergent cytopenic abnormalities (anemia as defined by hemoglobin < 10 g/dL, neutropenia as defined by absolute neutrophil count < 750 mm <sup>3</sup> or thrombocytopenia as defined by platelets < 50,000 mm <sup>3</sup> ) Proportion of subjects with on-treatment interferon-associated flu-like symptoms (as defined by pyrexia or chills or pain) Proportion of subjects with on-treatment musculoskeletal symptoms (as defined by arthralgia or myalgia or back pain) Proportion of subjects with SVR 24 weeks after treatment completion Proportion of subjects with on-treatment serious adverse events Proportion of subjects with dose reductions Proportion of subjects who discontinue due to adverse events Proportion of subjects with SVR 12 weeks after treatment completion in subjects with genotype-3 chronic HCV infection Proportion of subjects with on-treatment constitutional symptoms (fatigue or asthenia)
NCT01623336	Safety and Efficacy of BIP48 (Peginterferon Alfa 2b 48kDa) Compared With Pegasys® (Peginterferon 2a 40kDa) for Treatment of Chronic Hepatitis C: Randomized, Multicentric Study With Blinded Analysis.	BIP 48 (Pegylated interferon alfa-2b 48kDA) Pegylated interferon alfa-2a 40kDA BIP 48	Adult Senior	The rate of SVR measured by PCR 24 weeks after treatment completion Frequency of adverse events Virologic response at treatment completion

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01641640	A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 With Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naïve Subjects With Chronic Genotype 1, 4, 5, or 6 HCV Infection.	GS 7977 in combination with Pegylated interferon alfa-2a  Ribavirin	Adult  Senior	Efficacy 12 weeks after treatment completion  Safety and tolerability of GS-7977+Ribavirin+pegylated interferon alfa-2a when given for 12 weeks  Efficacy 4 and 24 weeks after treatment completion  Amount of circulating HCV RNA  Characterization of viral resistance
NCT01653236	Pilot Study to Determine the Efficacy and Safety of Combining Boceprevir With Peginterferon Alfa-2b and Ribavirin in the Treatment-naïve Patients Infected With Genotype 4 Chronic Hepatitis C Infection.	Boceprevir  Pegylated interferon alfa-2b  Ribavirin	Adult  Senior	Efficacy  Week 8 response  Week 12 response  IL-28B polymorphism
NCT01659567	Prospective Observational Study on Predictors of On-treatment Response and Sustained Virological Response in a Cohort of HCV-infected Patients Treated With Pegylated Interferons in Georgia.	Pegylated interferon alfa-2a  Pegylated interferon alfa-2b  Ribavirin	Adult  Senior	Predictive values of SVR  Correlation of patient characteristics and SVR  Overall treatment duration  Treatment duration after SVR  Correlation of treatment dose and SVR  SVR  Incidence of adverse events

NCT Number	Study Titles	Interventions	Age Groups	Outcome Measures
NCT01682720	A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977+ Ribavirin for 12 Weeks in Treatment Naive and Treatment Experienced Subjects With Chronic Genotype 2 or 3 HCV Infection.	GS-7977 Ribavirin Placebo	Adult Senior	Efficacy 12 weeks after treatment completion Safety and tolerability of GS-7977 + Ribavirin Efficacy 4 and 24 weeks after treatment completion Efficacy of treatment with GS-7977 + Ribavirin based on prior treatment history Kinetics of circulating HCV RNA during and after treatment completion Viral resistance to GS-7977 during and after treatment completion
NCT01687257	A phase 2, multicenter, open-label, randomized study to investigate the safety and efficacy of GS-7977 and ribavirin administered for 24 weeks in patients infected with chronic HCV with cirrhosis and portal hypertension with or without liver decompensation.	GS 7977 Ribavirin	Adult Senior	SVR 12 weeks after treatment completion Change in hepatic venous pressure gradient measurements Frequency and severity of adverse events
NCT01686789	Randomized Controlled Open Label Trial of Peg Alpha 2a Interferon and Adjusted-dose of Ribavirin vs. Standard Therapy in the Treatment of Naive Chronic Hepatitis C Patients Infected With Genotype 4.	Pegylated interferon alfa--2a Ribavirin	Adult Senior	SVR Requirement of blood-related products

Note: HCV=hepatitis C virus; PCR=polymerase chain reaction; RNA=ribonucleic acid; SVR=sustain virologic response.  
Source: Clinicaltrials.gov.