

Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Hepatitis C Treatment Adherence Interventions

I. Background and Objectives for the Systematic Review

Hepatitis C virus (HCV) infection is the most common chronic blood-borne infectious disease in the United States. The Centers for Disease Control and Prevention (CDC) estimates that 18,000 Americans were newly infected with the virus in 2008, and between 2.7 and 3.9 million people are living with chronic HCV infection.¹ Chronic HCV infection is associated with increased rates of cirrhosis, liver failure, and liver cancer and with 12,000 deaths per year in the United States. It is estimated that the direct medical costs of HCV-related diseases will top \$10 billion over the next 10 years.²

The prevalence of HCV infection is highest in non-Hispanic blacks when compared to all other ethnic groups and is highest in the 40–49 age group.³ The prevalence also increases with lower family income and less education. The transmission of HCV is primarily through large and repeated percutaneous exposure to infected blood.⁴ The most common mode of HCV transmission in the United States is the use of injection drugs. HCV can also be transmitted through needle-stick injuries and via vertical transmission from an infected mother to infant. The less common modes of transmission include sexual activities with an HCV-infected person and receipt of donated blood, blood products, and organs that are infected.⁴

The standard antiviral therapy for chronic HCV infection is the combination of pegylated interferon-alpha (alfa-2a or alfa-2b) with ribavirin. The therapy is typically administered for 24 weeks in patients infected with HCV genotype 2 or 3 and may be extended up to 48 weeks for patients with HCV genotype 1.^{5,6} The effects of antiviral therapies for HCV have been examined in a large number of randomized trials and systematic reviews.⁷⁻¹² These studies have consistently shown that the combination of pegylated interferon-alpha with ribavirin improves both sustained viral response and biochemical response and may improve histological response. In May 2011, the U.S. Food and Drug Administration (FDA) approved protease inhibitors (boceprevir and telaprevir) as a treatment for chronic HCV infection. These new agents may be used in combination with existing antiviral drugs, and the duration of treatment may change with the introduction of the new drug class.^{13,14}

Adherence to treatments has been shown to be important to the improvement of treatment outcomes and the reduction of adverse side effects for both infectious diseases and chronic diseases.¹⁵⁻¹⁸ Patients who are infected with HCV but are considered to be at high risk for treatment nonadherence, such as those with substance abuse or mental health disorders, may be excluded from treatment.¹⁹ It remains unclear, however, whether differential adherence to treatment is associated with varying treatment outcomes specifically in HCV antiviral therapy or whether treatment adherence interventions could impact intermediate and patient health outcomes.

Currently, no systematically reviewed evidence exists to reliably address these treatment adherence questions. A previous systematic review completed in 2004 for the U.S. Preventive Services Task Force included minimal discussion of treatment adherence.²⁰ It found that 14 to 22 percent of patients receiving the recommended combination therapy of pegylated interferon-alpha plus ribavirin discontinued treatment. Another review of antiviral treatment only

qualitatively summarized previous studies addressing adherence to HCV antiviral therapy; the findings of those studies were, however, inconsistent and inconclusive.²¹ Of the nine published guidelines for HCV management we identified, including the practice guideline of the American Association for the Study of Liver Diseases (AASLD), only one discussed treatment adherence but very briefly.²²

One particular issue in adherence intervention studies is the wide range of definitions used to describe treatment adherence. In the studies addressing treatment adherence for HCV antiviral therapy, the definition and measurement of treatment adherence has been variable. Some studies defined treatment adherence as the patient adhering to 80 percent or more of the total prescribed dose or to the prescribed treatment duration.²³⁻²⁵ The most commonly used definition of adherence appears to be the “80/80/80” rule, which is defined as greater than 80 percent adherence to the total number of ribavirin and interferon doses, taking greater than 80 percent of the required dosage of one or both drugs, for greater than 80 percent of the expected duration of therapy.²⁵ In addition, others may include the frequency and timing of administering each dose as components in defining measures of adherence.

Usually, treatment adherence includes medication adherence and regimen adherence. Medication adherence is defined as adherence by the patient to the dosing, duration, frequency, and timing of the prescribed medication. A lower level of adherence may be due to patient-initiated discontinuation of medications or poor quality of medication use (e.g., missing doses, reducing doses, inappropriate frequency and timing of use). Continued use of prescribed medication by the patient (i.e., without discontinuation) is often referred to as “persistence.” Health care providers may also initiate medication discontinuation or dose reduction, which is usually based on a medical plan or a desire to avoid treatment-related harms. Regimen adherence is defined as adherence by the patient to the prescribed followup visits, laboratory tests, or other medical procedures. In our study, we will consider both medication adherence and regimen adherence.

In addition, the terms used to define adherence varies across studies. Some of the terms used to describe patient adherence to medications and medical plans include “adherence,” “compliance,” “concordance,” “persistence,” and “patient cooperation.”²⁶⁻³⁰ These terms are sometimes used interchangeably in published studies. In our study, we will simply use the term “adherence.”

Known risk factors for nonadherence include previous substance abuse, psychiatric illness or cognitive impairment, the patient’s treatment experience or confidence in treatment, the patient-provider relationship, provider inexperience, the presence of comorbidities or anemia, and poor management of symptoms (side effects).^{18,20,31-33}

Various types of interventions aimed to improve adherence, and ultimately to improve treatment outcomes, have been studied. These may include more detailed instructions to patients (e.g., written instructions), increased communication and counseling (e.g., telephone followup, regular counseling programs, medication use training), increasing the convenience of medication use (e.g., simplifying drug dosing, tailoring the treatments to daily habits), using a reminder system (e.g., devices such as MEMS caps[®], appointment schedules, medication charts), and reinforcement or incentives for maintaining a high level of treatment compliance (e.g., simplifying clinic visits).³⁴⁻⁴⁰ These interventions may be used alone or in combination. In addition, interventions may be applied to both health care providers and patients to enhance the provider-patient relationship and the confidence of patients in their treatment success. Different

health care providers (e.g., nurses, physicians, and psychologists) in a variety of study settings (e.g., inpatient or outpatient setting, methadone clinic, etc.) have applied these interventions.

In this review, we propose to address the following:

1. We will assess the comparative effectiveness of treatment adherence interventions for adults receiving combination antiviral therapy for chronic HCV infection. The outcomes of interest include all-cause mortality, HCV-specific mortality, liver complications (cirrhosis, liver failure, and liver cancer), quality of life, transmission of HCV, sustained viral response, biochemical response (e.g., alanine transaminase [ALT] level), and histological response. We hypothesize that the treatment adherence interventions improve these outcomes.
2. We will also explore the association between differential adherence levels and health outcomes. We hypothesize that higher adherence levels are associated with improved health outcomes.
3. We will further explore the effectiveness of treatment adherence interventions in different subpopulations.

II. The Key Questions

We developed four Key Questions (KQs) with three subquestions and one contextual question to guide the literature search, data abstraction, and data synthesis for this topic. The proposed KQs were posted for public comment between June 27, 2011, and July 25, 2011, and were reviewed by a Technical Expert Panel (TEP), along with Key Informants who are known experts in the field. Based on the feedback received during the public comment period, KQ 3 was modified to include relapse rates as an intermediate outcome. An additional contextual question was also added to explicitly examine the varying definitions of adherence that are reported in the literature. The original KQs were not modified based on the feedback received.

The final proposed KQs for this review are:

Question 1

In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g., sustained viral response, histological changes, drug resistance, relapse rates, and treatment side effects) and final health outcomes (disease-specific morbidity, mortality, quality of life, transmission of HCV)?

- a. Does the comparative effectiveness of treatment adherence interventions differ by patient subgroups?

Question 2

In adult patients with chronic HCV infection undergoing antiviral therapy, is there an association between the level of treatment adherence and health outcomes?

Question 3

What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g., medication adherence; treatment plan adherence)?

- a. Does the comparative effectiveness of treatment adherence interventions in improving treatment adherence differ by patient subgroups?

Question 4

What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Contextual Questions

Note: These questions will not be systematically reviewed.

1. In adult patients undergoing antiviral treatment for chronic HCV infection, what factors are associated with patient nonadherence to treatment?
2. How is adherence defined in the medical literature about antiviral therapy for chronic HCV infection?

Identify for each KQ:

Population(s):

- Adults who are currently undergoing HCV antiviral therapy (combination therapy, including pegylated interferon with ribavirin or pegylated interferon with ribavirin and a protease inhibitor)

Interventions:

- Interventions that aim to increase adherence to antiviral therapy

Comparators:

- Standard care and/or other HCV treatment adherence interventions

Outcomes measures for each KQ:

- Intermediate health outcomes:
 - Early viral response (EVR)
 - Sustained viral response (SVR)
 - Histological changes
 - Biochemical response (ALT)
 - Drug resistance
 - Relapse rates
 - Adherence (frequency, dosage, treatment length, timing)

- Final health outcomes
 - Mortality (all-cause and HCV-specific)
 - Liver cirrhosis
 - Liver failure
 - Liver cancer
 - Quality of life
 - Transmission of HCV
- Adverse Effects
 - Paradoxical decrease in adherence
 - Increase in treatment-related harms
 - Patient burden, including psychological impact

Timing:

- Minimum followup of 12 weeks after baseline (to measure early viral response). Studies with longer followup times will be included, with attention paid to validity issues when pooling or conducting other analyses combining different time points.

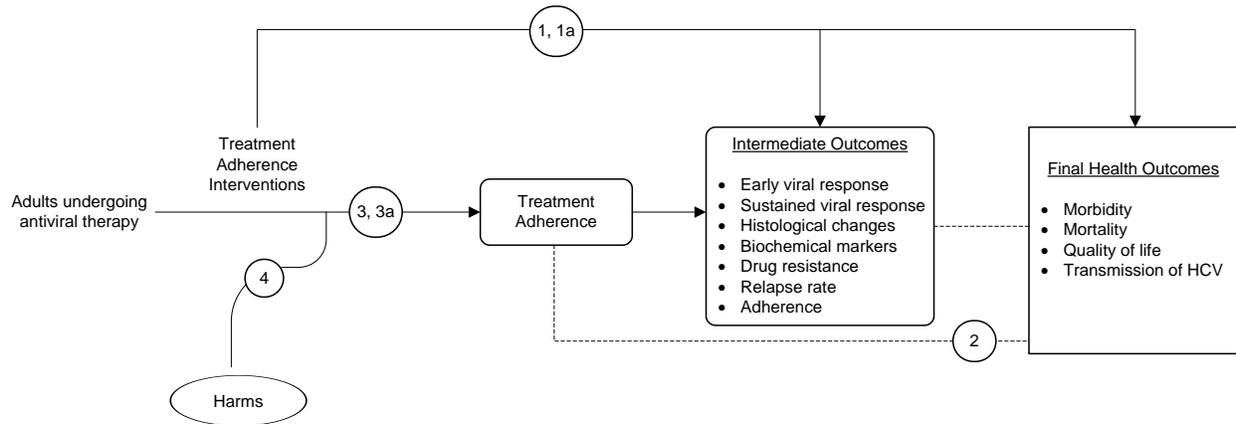
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III. Analytic Framework

Figure 1 provides an analytic framework to illustrate the population, interventions, and outcomes that will guide the literature search and synthesis. The figure depicts the KQs within the context of the PICOTS described in the previous section. In general, the figure illustrates how the adherence interventions may result in the improvement of intermediate and health outcomes and whether the interventions improve the level of adherence. The figure also depicts the possibility of adverse events occurring at any time after the adherence intervention begins.

Figure 1. Provisional analytic framework for evaluating the comparative effectiveness of treatment adherence interventions for adults undergoing HCV therapy



Abbreviations: HCV = hepatitis C virus

IV. Methods

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

We have developed a preliminary set of criteria for inclusion and exclusion of studies based on our understanding of the literature and discussions with Key Informants during the topic refinement phase (Table 1).

	Criteria	
	Include	Exclude
Population	Adults undergoing HCV antiviral therapy: <ul style="list-style-type: none"> ▪ Combination therapy with either pegylated interferon-alpha 2a or 2b and ribavirin ▪ Combination therapy with pegylated interferon, ribavirin, and protease inhibitors 	Adults undergoing: <ul style="list-style-type: none"> ▪ HCV monotherapy ▪ Adults undergoing long-term HCV maintenance therapy (>52 weeks of therapy) Children (≤18 years of age) <ul style="list-style-type: none"> ▪ Review focuses on adults only ▪ Excludes studies where >5% of the population is under the age of 18 years Excludes studies in which >5% of the population includes patients for whom treatment is contraindicated: <ul style="list-style-type: none"> ▪ Pregnant women ▪ Patients with renal failure ▪ Patients undergoing hemodialysis ▪ Transplant recipients
Intervention	KQs 1, 3, and 4 <ul style="list-style-type: none"> ▪ Treatment adherence interventions KQ 2 <ul style="list-style-type: none"> ▪ Adherence (or higher adherence level if 	

	treated as a continuous variable)	
	Criteria	
	Include	Exclude
Comparator	<p>KQs 1, 3, and 4</p> <ul style="list-style-type: none"> ▪ Other treatment adherence interventions or usual care <p>KQ 2</p> <ul style="list-style-type: none"> ▪ Nonadherence (or lower adherence level if treated as a continuous variable) 	
Outcomes	<p>KQs 1 and 2</p> <ul style="list-style-type: none"> ▪ All-cause mortality ▪ HCV-specific mortality ▪ Quality of life ▪ Transmission of HCV ▪ Liver transplants ▪ Liver complications <ul style="list-style-type: none"> ○ Cirrhosis ○ Liver failure ○ Liver cancer ▪ Change of HCV DNA from baseline ▪ Liver function (i.e., change of ALT level from baseline) 	<ul style="list-style-type: none"> ▪ Costs <ul style="list-style-type: none"> ○ Excludes studies in which cost is the only outcome reported
	<ul style="list-style-type: none"> ▪ Histological response (i.e., reduction in fibrosis) ▪ Early virological response ▪ Sustained virological response ▪ HCV relapse rates 	
	<p>KQ 3</p> <ul style="list-style-type: none"> ▪ Frequency ▪ Dosage ▪ Treatment length (duration) ▪ Timing 	<ul style="list-style-type: none"> ▪ Costs <ul style="list-style-type: none"> ○ Excludes studies in which cost is the only outcome reported
	<p>KQ 4</p> <ul style="list-style-type: none"> ▪ Adverse effects 	
Time Period	<p>2001 – present</p> <ul style="list-style-type: none"> ▪ First pegylated interferon was approved by the FDA in 2001 	Studies conducted prior to 2001
Setting	All Settings	None
Study Geography	Any	None
Language	English	
Study Design	<p>KQs 1–4</p> <ul style="list-style-type: none"> ▪ RCT of any design (i.e., parallel, crossover, factorial, cluster) ▪ Controlled clinical trial ▪ Prospective cohort study ▪ Retrospective cohort study ▪ Case-control study 	<ul style="list-style-type: none"> ▪ Single-case studies ▪ Cross-sectional ▪ Case series
Intervention Duration	Any	
Minimum Followup	<p>KQs 1–3</p> <ul style="list-style-type: none"> ▪ 12 weeks after baseline <p>KQ 4</p> <ul style="list-style-type: none"> ▪ Any 	

Study Quality	Any (good, fair, poor)	
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Abbreviations: ALT = alanine transaminase; FDA = U.S. Food and Drug Administration; HCV = hepatitis C virus; KQ = key question; RCT = randomized controlled trial

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

The research librarian, in collaboration with the investigative team, will develop and implement search strategies designed to identify evidence relevant to each KQ. An example proposed search strategy is shown in Appendix A. Comprehensive searches of the following databases will be conducted:

- MEDLINE[®] and PubMed[®]
- Cumulative Index to Nursing and Allied Health Literature (CINAHL[®])
- PsychINFO[®]
- Cochrane Central Register of Controlled Trials (CENTRAL)
- EMBASE[®]

The searches will be restricted to the English language and to the time period from January 2001 to the present. In 2001, pegylated interferon was approved by the FDA, which, in combination with ribavirin, became the standard of care. Comparisons of treatment adherence interventions before that date are not clinically relevant to current practice. The search is limited to the English language because it is not possible to obtain and translate non-English-language literature and stay within the expected timeline of the project. We will, however, run an ancillary search of the non-English-language literature so that we will know how many additional publications would have been reviewed if these studies were considered.

In addition, the research librarian will perform grey literature searches for this comparative effectiveness review. For the purposes of this review, the grey literature includes regulatory documents (e.g., FDA medical and statistical reviews; authorized medicines for the European Union), clinical trial registry entities (e.g., ClinicalTrials.gov), and conference abstracts (e.g., the American Association for the Study of Liver Diseases [AASLD] and its European equivalent). Additionally, we will request Scientific Information Packets from manufacturers of relevant drugs, devices, or programs, such as RibaPak[®] and MEMS[®] TrackCaps[™], to supplement the literature search.

We will also examine the reference lists of reviews and guidelines to identify potential studies for inclusion. We will retrieve original studies identified by screening reference lists. We will also supplement our searches with suggestions from members of the TEP.

We will conduct an initial search, followed by at least one bridge search while the draft report is undergoing review, and will add relevant references as needed. Additionally, we will incorporate references that are of particular relevance for the background sections. Results from the literature searches will be entered into version 11.0.1 of Reference Manager[®] (Thomson Reuters, New York, NY), a bibliographic management database.

C. Data Abstraction and Data Management

Study Selection

We will apply a two-step process for study selection. First, two reviewers will independently review the title and abstract of each article to determine if an article may meet the broad inclusion/exclusion criteria (Table 1). Each article will be coded as: potentially included (I), excluded (E), or background material (X). Then, we will retrieve full-text articles for all potentially eligible studies, including those that are questionable or unclear at the abstract stage. Two reviewers will independently assess each full-text article using a standard form that details the predetermined inclusion and exclusion criteria. Once the team receives the grey literature search results from our librarian, we will review abstracts and/or full-text articles according to the protocol described above and will match them to published studies, noting any discrepancies between sources.

Data Collection

Data from all included studies will be abstracted into standard evidence tables by one abstractor and checked for accuracy and completeness by a second abstractor. We will obtain the following information from each study as available:

- *Background information*: author identification, year of publication, and source of study funding.
- *Study characteristics*: type of study (randomized controlled trial [RCT], nonrandomized controlled trial, prospective cohort study, retrospective cohort study, case-control study), whether the study randomized individual patients or clusters of patients, study setting, sample size, geographic area of study, and number of study centers. If a study is an RCT, we will also record the study design (i.e., parallel, crossover, and factorial) and decide whether the study randomized individuals or clusters of participants.
- *Patient characteristics*: age, sex, ethnicity, socioeconomic status, HCV genotype, current or previous substance abuse, treatment-naïve vs. retreated, mental illness, education, and comorbidities.
- *Treatment regimens*: prescribed antiviral therapy. We will record the generic names of the drugs used to treat the intervention and control groups, dose, dosage forms, timing, and duration of each prescribed treatment. We will also record the setting of medical care (e.g., inpatient, outpatient).
- *Interventions and controls*: type of adherence interventions, duration, intensity, and definition of adherence for each. Details about types of adherence interventions are described in the introduction.
- *Definitions and measure of adherence*: we will document the adherence definitions used in each study, including medication adherence, regimen adherence, or both; components of medication adherence (e.g., dose, frequency, duration, timing); components of regimen adherence (e.g., followup visits, laboratory tests); cut-off value for defining adherence; measure of adherence (e.g., pill counts, rates of prescription refills, patient questionnaire).
- *Outcomes*: sustained viral response (SVR), histological response, biochemical response (i.e., ALT level), drug resistance, all-cause mortality, disease-specific mortality, liver cirrhosis, liver failure, liver cancer, quality of life, and transmission of HCV. We will record authors' definitions of SVR, drug resistance, histological response, and quality of life.

- For RCTs, controlled trials, and cohort studies, we will record, for each group, the number of events, the number of patients allocated, and the number of patients lost to followup. We will document what methods the authors used to deal with loss to followup and the resulting estimates, including effect measures, point estimates, 95 percent confidence intervals (95% CIs), and *p*-values.
- For case-control studies, we will record the numbers of cases and control subjects and the number of exposures (i.e., receiving adherence interventions) for each group. We will document the results reported by the authors, including effect measures, point estimates, 95% CIs, and *p*-values.

The basic elements and design of the evidence table will be the same as multiple tables previously tested for other systematically reviewed topics. We will test the table on selected high-quality studies and will revise it as necessary before data abstraction is fully performed on all articles. Authors of included studies will be contacted for clarifying methods (e.g., randomization methods) or results (e.g., providing missing data or verifying the data) if necessary.

Review Management

All reviewers will check the consistency between their decisions and will resolve disagreements through discussion or third-party adjudication if needed. To ensure a high level of consensus, all reviewers will do a pilot study exercise, screening the title and abstract of 30 articles and the full text of 5 articles and abstracting data from 2 to 3 articles. A member of the team will abstract the articles, and they will be dually reviewed to ensure accuracy and completeness. We will code the reason any articles, at the stage of the full-text review, are not included in the review. Studies at the abstract and full-review stage will be managed with Reference Manager so that we can easily compile a list of included and excluded articles and the reasons for exclusion. Project staff will meet regularly to discuss the results at each phase, to review studies that are difficult to classify, and to address any questions that the team may have.

D. Assessment of Methodological Quality of Individual Studies

To assess the methodological quality of included studies, we will use a set of modified criteria developed by the U.S. Preventive Services Task Force.⁴¹ Two independent reviewers will assign a quality rating of the internal validity for each study. Disagreements will be resolved by discussion and consensus or by consulting a third, independent reviewer. A rating of “good,” “fair,” or “poor” will be assigned by using the predefined criteria for each study design. Such criteria include: adequate randomization methods (for RCTs), consideration of potential confounders, maintenance of comparable groups, reliable and valid measurements, clear definition of interventions, and appropriate analyses (e.g., intention-to-treat analysis for RCTs). Generally, a good-quality study meets all criteria for that study design; a fair-quality study does not meet all criteria but is judged to have no major flaw that invalidates its results, such as a substantial loss to followup or failure to conceal treatment allocations; and a poor-quality study contains a fatal flaw. In addition, the quality assessment of adverse effects and harms data will be informed by the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*⁴² (hereafter *Methods Guide*) developed by the Agency for Healthcare Research and Quality.

Quality ratings will be recorded in the evidence tables. No studies will be excluded based on this quality assessment, although the impact of quality assessments on outcomes will be explored during data synthesis.

E. Data Synthesis

Presentation of Individual Studies

For each KQ, we will present the information about study setting (e.g., country of study), study design, sample size, study quality, patient characteristics, adherence interventions, controls, and outcomes data in a grand evidence table. On the basis of study characteristics, study quality, precision of estimates, and magnitude of effects, we will assess whether the study can provide valid and applicable results to the population of interest.

Quantitative Analyses

Key Questions 1, 3, and 4

We will assess whether the included studies are homogenous enough in clinical (e.g., patient characteristics, interventions) and methodological (e.g., study design, risk of bias, definition of adherence, outcome measurement) characteristics.

We will undertake meta-analyses of studies where appropriate for the outcomes listed below. We will use the random-effect model to pool studies separately by study designs (i.e., RCTs vs. nonrandomized clinical trials or observational studies). We will report the risk ratio and 95% CI of pooled estimates for the binary outcome and the mean difference and 95% CI for the continuous outcome.

- All-cause mortality:
- HCV-specific mortality
- Quality of life
- Transmission of HCV
- Liver transplantation
- Development of cirrhosis
- Development of hepatocellular carcinoma
- Virological response (i.e., undetectable HCV DNA)
- Change in HCV DNA from baseline
- Biochemical response (i.e., ALT level below upper normal limit)
- Change in ALT from baseline
- Histological response
- Early viral response
- Sustained viral response
- Disease relapse
- Development of any viral resistance
- Frequency (number of times per day/week a drug is taken)
- Dosage (patient/self-directed dose reduction)

- Treatment length (duration of treatment; if the patient completes all 24 or 48 weeks of treatment)
- Timing (timing of drug doses; protease inhibitors are scheduled to be taken within a strict time-window)

We will also use the heterogeneity chi-square test and I-square statistic to examine statistical heterogeneity. We define heterogeneity as small if the I-square statistic is less than 25 percent, as moderate if it is between 25 percent and less than 50 percent, and as substantial if 50 percent or more.

We will undertake subgroup analyses to explore heterogeneity among studies irrespective of the magnitude of the I-square statistic. To avoid spurious findings, we will use a small number of prespecified hypotheses to explore heterogeneity. The following is a list of potential variables:

- Current or former substance use
- Mental illness
- Comorbidities (e.g., HIV infection)
- Duration of antiviral therapy
- Definition of adherence
- Length of adherence interventions
- Socioeconomic status
- Patient confidence in treatment

We will also examine the robustness of the pooled results using the following options:

- Using an alternative effect measure (i.e., odds ratio)
- Excluding poor-quality studies

Key Question 2

We will undertake a multivariable meta-regression analysis to examine the association of each adherence intervention versus no adherence intervention with each of the following outcomes:

- HCV-related mortality and all-cause mortality
- Transmission of HCV
- Liver transplantation
- Development of cirrhosis
- Development of hepatocellular carcinoma

In the meta-regression, we will treat the log-risk ratio of the outcome as a dependent variable and include the following as independent variables:

- Type of adherence intervention
- Type of medication
- Type of study design (RCT vs. nonrandomized studies)

- Risk of bias (good or fair vs. poor)
- Length of adherence intervention
- Length of study followup

As a rule of thumb, valid estimates require 10 studies per category. We anticipate that the number of included studies will be small, so we may consider dropping variables for the meta-regression analyses by following these hierarchical rules: drop length of study followup > length of adherence intervention > type of medication > risk of bias > type of study design.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for primary outcomes using the standard process of the Evidence-based Practice Centers as outlined in the *AHRQ Methods Guide*.⁴³ The grade will be based on four major domains: risk of bias, consistency, directness, and precision of the evidence. We will classify the bodies of evidence pertaining to each primary outcome into four basic grades: high, moderate, low, and insufficient (Table 2). As advised in the *AHRQ Methods Guide*, the number of studies that form that basis of given findings or conclusions will also be recorded. Additional domains—such as dose-response association, plausible confounding, strength of association, and publication bias—will be assessed and reported as appropriate.

Table 2. Strength of evidence grades and definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

G. Assessing Applicability

Judgments of applicability for each outcome (including harms) will be performed separately from assessments of the other domains of strength of evidence as recommended in the *AHRQ Methods Guide*.⁴³ We will identify and abstract factors in individual studies that might affect applicability, particularly including factors related to the populations—for example, how highly select they were (what portion of those recruited were randomized), how they were recruited (whether the participant contacted the study staff in order to be included vs. individual outreach to potentially eligible participants by the study staff, etc.), and the intervention they received (whether there were multiple interventionists, the level/degree of training among interventionists, whether there was a clearly defined protocol, etc.). Based on these characteristics, we will note any potential limitations to applicability on the interpretation of each individual study and will

conclude with an evaluation of the applicability of the total body of evidence. In addition to describing these characteristics of the included trials, we will examine these features when data are sufficient to see if they appear to affect effect size. If appropriate, we will summarize important applicability issues in table format.

V. References

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

Date	Section	Protocol Deviation	Rationale
04/16/2012	II. Key Questions (KQs)	Change KQ 2 to a new contextual question (contextual question 3; Appendix B).	The body of literature available to answer this question is small, of poor quality, with high heterogeneity. Although we had a research librarian conduct the search, treatment adherence is usually not the primary purpose of the primary literature, making it extremely challenging to identify studies that can answer this question. We will use the literature identified by our expert librarian search to answer the question in a contextual manner; this will ensure that the literature included was found from a broad, well-designed search, but will provide a more useful answer to end-users of the review than a quantitative estimate of the relationship between adherence and outcomes.
04/16/2012	II. KQs	Renumber the KQs. The revised KQs and contextual question are attached (Appendix B).	The original KQ 2 has been changed to a contextual question.
04/16/2012	II. Analytic Framework	Revise the analytic framework to reflect the removal of KQ 2 (Appendix C).	The original KQ 2 has been changed to a contextual question.
04/16/2012	IV. Methods/ Inclusion and Exclusion Criteria	Remove criteria specific to previous KQ 2. The revised criteria table is attached (Appendix D).	The original KQ 2 has been changed to a contextual question.
4/16/2012	IV. Methods/Data Synthesis	Remove language regarding the data analysis plan for KQ 2.	The original KQ 2 has been changed to a contextual question.

Additional References

1. Ghany MG, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011 Oct 1;54(4):1433-44. PMID: 21898493.
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VIII. Review of Key Questions

For all EPC reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness Reviews, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

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

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

Appendix A: Example Draft MEDLINE Search Strategy

- 1 Hepatitis C/ (27027)
- 2 Hepatitis C, chronic/ (12331)
- 3 Hepacivirus/ (18867)
- 4 1 or 2 or 3 (44130)
- 5 Patient compliance/ (40163)
- 6 Medication adherence/ (2445)
- 7 "Patient Acceptance of Health Care"/ (24667)
- 8 Patient participation/ (14782)
- 9 Patient satisfaction/ (47132)
- 10 Patient preference/ (686)
- 11 Treatment refusal/ (9693)
- 12 5 or 6 or 7 or 8 or 9 or 10 or 11 (132248)
- 13 4 and 12 (389)
- 14 limit 13 to (controlled clinical trial or randomized controlled trial) (20)
- 15 hepatitis c.ti,ab. (41595)
- 16 hepacivirus.ti,ab. (41)
- 17 HCV.ti,ab. (30101)
- 18 15 or 16 or 17 (47201)
- 19 adhere\$.ti,ab. (87561)
- 20 comply\$.ti,ab. (6979)
- 21 compliance.ti,ab. (64903)
- 22 complies.ti,ab. (675)
- 23 noncomplan\$.ti,ab. (5342)
- 24 nonadheren\$.ti,ab. (5024)
- 25 patient cooperation.ti,ab. (560)
- 26 medication persistence.ti,ab. (41)
- 27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (161047)
- 28 18 and 27 (745)
- 29 limit 28 to ("in data review" or in process or "pubmed not medline") (54)
- 30 (random\$ or placebo\$.ti,ab. (600997)
- 31 29 and 30 (9)
- 32 14 or 31 (29)
- 33 limit 32 to english language (29)
- 34 remove duplicates from 33 (29)

Appendix B: Revised Key Questions and contextual questions

Key Questions

Question 1

In adult patients with chronic HCV infection undergoing antiviral therapy, what is the comparative effectiveness of treatment adherence interventions in improving intermediate (e.g.

sustained viral response, histological changes, drug resistance, relapse rates, and treatment side effects) and final health outcomes (disease-specific morbidity, mortality, quality of life, transmission of HCV)?

- a) Does the comparative effectiveness of treatment adherence interventions differ by patient subgroups?

Question 2

What is the comparative effectiveness of treatment adherence interventions in improving treatment adherence (e.g. medication adherence; treatment plan adherence)?

- a) Does the comparative effectiveness of treatment adherence interventions in improving treatment adherence differ by patient subgroups?

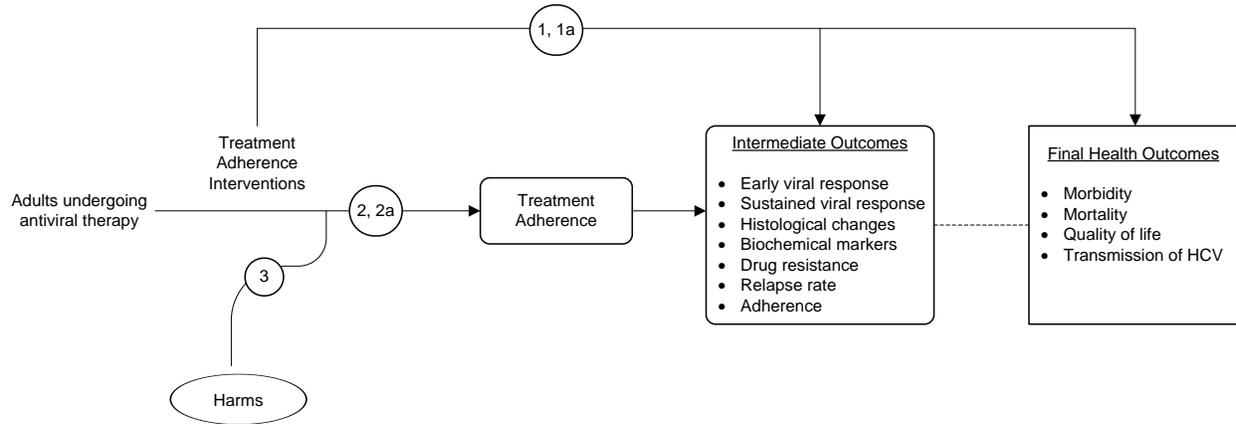
Question 3

What are the harms associated with hepatitis C antiviral treatment adherence interventions?

Contextual questions

1. In adult patients undergoing antiviral treatment for chronic HCV infection, what factors are associated with patient nonadherence to treatment?
2. How is the adherence defined in the medical literature about antiviral therapy for chronic HCV infection?
3. In adult patients undergoing antiviral treatment for chronic HCV infection, what is the association between treatment adherence and outcomes, and how is that modified by other factors?

Appendix C: Revised analytical framework



Appendix D: Revised criteria for inclusion and exclusion of studies in the review

	Criteria	
	Include	Exclude
Population	<p>Adults undergoing HCV antiviral therapy:</p> <ul style="list-style-type: none"> ▪ Combination therapy with either pegylated interferon-alpha 2a or 2b and ribavirin ▪ Combination therapy with pegylated interferon, ribavirin, and protease inhibitors 	<p>Adults undergoing:</p> <ul style="list-style-type: none"> ▪ HCV monotherapy ▪ Adults undergoing long-term HCV maintenance therapy (greater than 52 weeks of therapy) <p>Children (≤ 18 years)</p> <ul style="list-style-type: none"> ▪ Review focuses on adults only ▪ Exclude studies where $>5\%$ of population is under the age of 18. <p>Exclude studies where $>5\%$ of population include patients for whom treatment is contraindicated:</p> <ul style="list-style-type: none"> ▪ Pregnant women ▪ Patients with renal failure ▪ Hemodialysis patients ▪ Transplant recipients
Intervention	<ul style="list-style-type: none"> ▪ Treatment adherence interventions 	
Comparator	<ul style="list-style-type: none"> ▪ Other treatment adherence interventions or usual care 	
Outcomes	<p>KQ 1</p> <ul style="list-style-type: none"> ▪ All-cause mortality ▪ HCV-specific mortality ▪ Quality of life ▪ Transmission of HCV ▪ Liver transplants ▪ Liver complications <ul style="list-style-type: none"> ○ Cirrhosis ○ Liver failure ○ Liver cancer ▪ Change of HCV DNA from baseline ▪ Liver function (i.e., change of ALT level from baseline) ▪ Histological response (i.e., reduction in fibrosis) ▪ Early virological response (EVR) ▪ Sustained virological response (SVR) ▪ HCV relapse rates 	<ul style="list-style-type: none"> ▪ Costs <ul style="list-style-type: none"> ○ Exclude studies where cost is the only outcome reported
	<p>KQ 2</p> <ul style="list-style-type: none"> ▪ Frequency ▪ Dosage ▪ Treatment length (duration) ▪ Timing 	<ul style="list-style-type: none"> ▪ Costs <ul style="list-style-type: none"> ○ Exclude studies where cost is the only outcome reported

	Criteria	
	Include	Exclude
	KQ 3 ▪ Adverse effects	
Time Period	2001 – present ▪ First pegylated interferon was approved by the FDA in 2001	Studies prior to 2001
Setting	All Settings	None
Study Geography	Any	None
Language	English	
Study Design	<ul style="list-style-type: none"> ▪ RCT of any design (i.e. parallel, crossover, factorial, cluster) ▪ Controlled clinical trial ▪ Prospective cohort study ▪ Retrospective cohort study ▪ Case-control study 	<ul style="list-style-type: none"> ▪ Single case studies ▪ Cross-sectional ▪ Case series
Intervention Duration	Any	
Minimum Followup	KQ 1-2 <ul style="list-style-type: none"> ▪ 12 weeks after baseline KQ 3 <ul style="list-style-type: none"> ▪ Any 	
Study Quality	Any (good, fair, poor)	