Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Interventions To Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness*

Draft review available for public comment from July 11, 2012 to August 8, 2012.

Research Review Citation: Sun X, Patnode CD, Williams C, Senger CA, Kapka TJ, Whitlock EP. Interventions To Improve Patient Adherence to Hepatitis C Treatment: Comparative Effectiveness. Comparative Effectiveness Review No. 91. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 13-EHC009-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or email. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Source: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1363
Published Online: December 20, 2012

Commentator & Affiliation	Section	Comment	Response
FDA	Executive Summary	On page ES-1, An addition to this introduction may be improved with the inclusion of a notation that outcome of treatment improved with the development/usage of pegylated IFN. Most notably and relevant are the improvement in adherence issues that were associated with the improved regimen over the non-pegylated IFN regimen.	We did not feel it was within the scope of this review to summarize the improvements seen in adherence or treatment according to the changes in standard of therapy over time. We felt it was most important to discuss the current standard(s) of therapy (i.e., dual therapy with pegylated IFN and triple therapy with protease inhibitors).
TEP #5	Executive Summary	Page 9, line 12: The authors might want to cite Chak et al (2011) [which is found in the main document but not in the ES], which projects up to 7.1 million individuals in the U.S. potentially infected with HCV. The quoted 2.7-3.9 from NHANES is likely an underestimate.	Thank you for catching this. We added the suggested citation to the ES.
TEP #5	Executive Summary	Page 9, line 21: Genotypes (1-4) may not be the sole "best" predictor of viral response anymore, as was once cited in Ghany, 2009. More recent genetics research demonstrates that among patients with genotype 1 (75% of the population), the IL28b genetic polymorphism now predicts over 50% of the variance in treatment response (see Thompson et al, 2010, *Gastro; Ge, 2010)*.	We have revised this sentence to read that genotyping is *among* the best ways to predict response.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary	Page 9, Line 44-54 (as well as in the main document and Table 2 on page 37): While I appreciate the ease at which the authors can apply *a priori* categories, which may have been appropriate to other medical treatments and/or populations, components of this system seem a bit clunky as applied to HCV treatment. It's reasonable to keep the policy-level category even though no studies currently exist. An artificial distinction is made between #4 "patient-level interventions" and #5"interventions designed to help manage adverse side effects." Both of these categories represent interventions aimed at the patient-level so dividing them seems arbitrary and confusing. I might propose keeping only the "patient-level" category and then subsuming category #5 under the "patient level" category. Then, under patient-level interventions, the authors could create 2 subcategories: pharmacological and nonpharmacological interventions. The Bertino et al 2010 and Morasco et al 2010, which are probably linked moreso to *treatment completion rates* rather than *medication adherence* per se, would be captured under pharmacological interventions. Nonpharmacological interventions could capture the two categories of adherence interventions that were recently described in the 2012 HIV Guidelines (i.e., behavioral/structural reminder systems; education/counseling for individuals or groups (see *Thompson et al, Guidelines for Improving… Adherence for Persons With HIV: Evidence-Based Recommendations From an International Association of Physicians in AIDS Care Panel. Ann Intern Med 2012*). (see the next page)	The reviewer proposed to classify the patient-level interventions by pharmacological versus non-pharmacological strategies. Although this may represent an alternative classification approach, we don't find this method is superior to our current classification or improves readability. We developed the categories according to the underlying mechanisms of action. We agree that interventions for managing adverse events may be considered patient-level interventions. However, adverse events of medications represent an important and independent domain for patient non-adherence in hepatitis C treatment. Thus, we consider it reasonable and important to separate these interventions from other patient-level interventions. (more response in the next page)

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary	Additionally, any behavioral, psychological, peer group, or coping skills training interventions (e.g., Ramsey et al 2011) aimed at "helping to manage adverse side effects", which probably target persistence (i.e., treatment completion), could also be captured under nonpharmacological interventions. Similarly, the information displayed in Table 2 (page 37) under patient-level and adverse effect management should be divided into nonpharmacological and pharmacological interventions. Among the nonpharmacological interventions, the authors may be able to further dissect them into the use of behavioral reminder systems (i.e., activities that require minimal education and counseling) and educational, supportive or psychological treatments. This revision may be a) more precise, informative, and useful for end users; b) lend itself to a more useful discussion of patient-level interventions which the authors currently struggle with on page 21, lines 45-52; and c) may help stimulate future research efforts to develop both pharmacological and nonpharmacological interventions at the patient level, and better differentiate between behavioral reminder systems, education/counseling to improve dosing behaviors, and interventions to manage side effects (e.g., Thompson et al AIM, 2012).	We agree on the possibility of further dividing the patient-level interventions into finer categories (e.g. educational, supportive, etc). However, given the paucity of evidence about patient-level adherence interventions and the lack of detail regarding each intervention, we did not further categorize the interventions.
TEP #5	Executive Summary	The authors do not include a category for interventions at the provider-level, which should be included somewhere. While provider-level interventions may be captured under "system-level" or "patient-level" interventions, they probably fit better in their own category. Like the policy-level category, I am not aware of any provider-level interventions that currently exist in HCV, however, creating a category for them or at least including them in the table of interventions could stimulate interest in developing and evaluating such interventions. Interventions to improve provider-level behaviors (e.g., shared decision-making process, psychoeducational communication style, use of motivational enhancement techniques) could improve patient adherence to both medication-taking and completion of treatment. Interventions to improve providers' expertise and training could also improve pharmacological management of side effects and, in turn, improve treatment completion rates.	This is a good suggestion. We have added a row to Table 2 to describe provider-level interventions as another category of interventions and added a note in the results section that states that no studies that evaluated the effect of a provider-level intervention were included in the review.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary	Federal agencies (U.S. DHHS 2010; CDC) strongly encourage the use of multidisciplinary or integrated team approaches to improve the care and treatment of patients with HCV, many of whom have mental health and substance use disorders. Although there have been no RCTs to test team approaches compared to usual care, it is likely that implementation of multidisciplinary teams will have a profound impact on our ability to successfully treat more patients. RCTs or observational studies with comparator groups should be encouraged to evaluate the impact of multidisciplinary team approaches on medication adherence, treatment plan adherence, management of side effects, and treatment completion rates. Several good cohort studies exist at this point, but they have not been tested in clinical trial designs. This type of health services research would fit well under 'system-level" interventions and should be included in the text or in Table 2, page 37. This type of system-level change seems to be gaining momentum and federal agency support, so it is worth folding into examples of system-level interventions.	We reviewed the list of cohort studies that this reviewer sent. We double checked and these studies were all screened or reviewed in full-text and were excluded based on our *a priori* eligibility criteria.
TEP #5	Executive Summary	Throughout the review, the authors use the term "adverse effects"—it may be more appropriate and consistent with the HCV literature to use another term such as "adverse side effects" "adverse events", or "side effects."	Thank you for this suggestion. We have replaced adverse effects with "adverse events" throughout the document.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary-Introduction	The authors need to define the global term of "adherence" better, and early in the paper. Terms like "patient adherence," "treatment adherence" and "adherence" are used interchangeably, and there are other terms used like "medical adherence" and "treatment plan adherence." They attempt to define "treatment adherence" (page 10, line 28) by giving examples of "medication adherence" and "treatment plan adherence" but these definitions need to come earlier. The reader is often confused up until this point. Are these interventions to reduce missing doses, improve persistence, or increase doctor visits? This distinction is important because the type of interventions needed to target dosing behaviors will be distinctly different than those interventions needed to help patients complete treatment. Perhaps they can chose a global term like "patient adherence" to use consistently throughout the paper, but clarify early in the ES that "patient adherence" may incorporate "medication adherence" and/or "protocol," "treatment," or "medical" adherence (chose one). They need to choose one global adherence term, be consistent with its usage throughout the paper, and apply the more precise terms of medication adherence or protocol adherence, when it is necessary. *The authors might review the following: 1) Urquhart and Vrijens (2005), Euro J Hosp Pharm Sci; Vrijens et al (2008), BMJ; Evon et al (2012) JCCP.*	We agree that this is very confusing. We have changed the text to clarify that our definition of "adherence" (now termed patient adherence or "adherence" more generally) refers to both adherence to one's medication and adherence to the full medical plan. We feel that the placement of this discussion is in the appropriate place within the ES and full report. However, we have changed the title of the report to reflect patient adherence.
TEP #5	Executive Summary-Introduction	Page 10, Figure A, here is an example of confusion about the definition. There is a box labeled "treatment adherence" and then "adherence" is mentioned again in the "Intermediate outcomes" box—how can adherence lead to adherence and what is the difference?	We revised Figure A in the ES and Figure 1 in the full report.
TEP #5	Executive Summary-Introduction	Page 10, Figure A, under Intermediate Outcomes: please clarify that "relapse rate" means "viral relapse" and not "alcohol or drug relapse," the latter of which could be construed as nonadherent behavior during treatment	We revised Figure A in the ES and Figure 1 in the full report.
TEP #5	Executive Summary-Methods	The inclusion and exclusion criteria are justifiable, though fairly stringent given the paucity of data. The search strategies are explicitly stated and logical. The definition of adherence needs improvement, as mentioned above. The definitions of the various outcome measures are appropriate, though focus on final health outcomes seems premature	Based on several comments related to the focus on final health outcomes, we reduced the emphasis on long-term health outcomes, and suggested the need for confirming the effect on intermediate outcomes in the Research Gaps section.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary-Methods	Page 11, line 32: again the term "treatment adherence" seems misleading here given the descriptive in the parentheses. Perhaps authors mean "medication adherence"? If they decide to choose "treatment adherence" perhaps need to include other forms of patient nonadherence (noncompliance with the regimen, drop-out or premature treatment discontinuation) in parentheses.	As indicated above, we are now using "patient adherence" or "adherence" generally to reflect patient noncompliance and patient-led treatment discontinuation. This could include reductions in the dose, duration, frequency, timing, or a combination of these factors.
TEP #5	Executive Summary-Methods	Page 11, Line 54: "loss to followup" of subjects in an adherence study can be interpreted as an outcome. Please make sure that if any studies were faulted or deemed poor quality due to having loss to followup, that this could not be construed as a study outcome (i.e., nonadherence to the treatment protocol).	We agree that this can be confusing. We did not include patients for whom treatment was discontinued as being lost-to-followup. We only considered patients as being lost-to-followup if there were no data available (including that their treatment was discontinued).
TEP #5	Executive Summary-Methods	Page 11, line 54: Do the authors mean subject blinding or investigator blinding? It would be nearly impossible to blind subjects to adherence outcome assessments, since medication adherence measurements require subjects to complete pill-taking diaries, bring in pill bottles for pill counts, or receive training in electronic monitoring devices.	We assessed patient blinding, provider blinding, and outcome assessor blinding. We clarified this in the methods section of the ES and full report. We agree that patient blinding (to the intervention assignment) is difficult to achieve in these trials. However, failure to achieve blinding increases the risk of bias. No studies were rated as poor quality strictly on the basis of blinding of the patients, providers, or outcome assessors.
TEP #5	Executive Summary-Methods	Page 11, line 20: Reconsider need to assess "relapse rates" since this would be captured under other treatment outcomes like SVR. Patients' treatment outcomes are typically categorized as "Nonresponders," "Relapsers" OR "SVR," so to investigate "relapse rate" seems redundant with SVR.	These two outcomes, although similar, have different clinical implications. Thus, we included both outcomes. We did not identify any study reporting virological relapse rate.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary-Methods	Regarding the decision to investigate final health outcomes, it would be premature for the science of adherence intervention studies to explore associations with mortality and morbidity, when the association with SVR (the necessary intermediate outcome) is weak and insufficient. Additionally, it has only been recently that adequate evidence supports a relationship between SVR and morbidity and mortality rates. Therefore, in several sections of the CER, it is important to focus recommendations on establishing a reliable and consistent link between adherence interventions and SVR first before allocating resources to collecting distal final outcomes. High-quality studies that explore moderators, mediators and interaction effects are needed to better understand how and for whom such interventions lead to higher SVR rates.	As a systematic review, it is important to systematically identify all relevant evidence about the effect of adherence interventions, including those addressing both surrogate outcomes (e.g. SVR) and health outcomes. This study provides important information regarding gaps for future research in both types of outcomes. We added additional text that emphasizes the importance of understanding the association between adherence and SVR and have de-emphasized the focus on final health outcomes.
TEP #5	Executive Summary-Results	The amount of detail presented in the results section is appropriate. The characteristics of the studies are clearly described. The selection of the 11 studies for the review is appropriate. Flow diagram of decision-making for exclusion seems appropriate.	Thank you for this comment. No response necessary.
TEP #5	Executive Summary-Results	Page 14, line 28: Given minimal differences (e.g., duration) in clinical treatment of acute HCV vs. chronic HCV, if these two studies otherwise met inclusion criteria, they might be re-considered for analysis.	We pre-specified that studies of acute hepatitis C would be not be included in this review given the apparent clinically different prognosis between acute and chronic HCV, and the differential strategies for managing these two conditions.
TEP #5	Executive Summary-Discussion	The implications of the major findings are clear. The limitations of the review are described adequately. The future research section is clear, logical and useful to stimulate new research in HCV adherence.	Thank you. No response necessary.
TEP #5	Executive Summary-Discussion	Page 21, line 48: If no studies evaluated behavioral reminder systems, a technique commonly tested in other medical populations (Thompson et al, AIM, 2012) please state this. It may stimulate research in this area, especially given that triple therapy dosing is 3-4 times per day and clinically, reminder systems are essential.	We did not identify any studies that evaluated the use of reminder systems. We have added a sentence in our discussion of future research needs that notes the importance of such studies.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary-Discussion	Page 26, line 7: Although studies of dual therapy are not directly applicable to triple therapy regimens, it's reasonable to make a case to extrapolate from these studies indirect evidence that medication adherence (and perhaps even persistence/completion) will likely worsen during triple therapy given the consistent dose-response relationship found in the broad medication adherence literature (Claxton et al 2001, Clin Ther).	We agree with this extrapolation and included a sentence (line 11) that states, "In particular, adding a third agent administered multiple times per day is likely to further impact patients' ability and likelihood of complying with treatment." Additional detail regarding this point was also provided in the Applicability section of the full report.
TEP #5	Executive Summary-Discussion	Page 26, lines 17-21: Good point made that these data do not apply to many cohorts of individuals infected with HCV who are deferred from antiviral therapy (e.g., active substance abuse or psychiatric instability), but who may be at risk for worse adherence outcomes.	Thank you, we thought this was an important point as well. No response necessary.
TEP #5	Executive Summary-Discussion	Page 26, lines 28-30: The authors might encourage researchers to avail intervention protocols online or publish manuscripts of intervention development so that they can be further tested and disseminated in real-life settings.	We decided not to include this recommendation in the ES due to the limited space. We added a sentence encouraging authors and journal editors to publish these details in the Future Research Section of the full report.
TEP #5	Executive Summary-Discussion	Page 26, Lines 40-42: Again, attenuate the emphasis on long-term final health outcomes. This push is premature given insufficient evidence of an association with adherence behaviors and SVR rates. Please encourage more studies of proximal outcomes.	This is a good suggestion. We modified our future research recommendation to reduce the emphasis on long-term outcomes, and suggested the need to confirm the effect of interventions on intermediate outcomes (e.g. SVR); however, we still feel that this is an important issue to address in this field.
TEP #5	Executive Summary-Discussion	Page 26, lines 51-55: This is an excellent point that needs highlighting and may need to come early in the Discussion, Research Gaps or both sections. Given their current expertise in this area, do the authors want to make any suggestions regarding definitions that may be most useful for HCV adherence researchers moving forward?	We agree that this is a very important point to make and have left it in the Research Gaps section. We think it is more appropriate for HCV experts and adherence experts to define adherence in the HCV field. We believe this review provides useful information for this purpose.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Executive Summary-Discussion	Page 27, lines 7-8: In line with previous suggestion, "through medication and counseling methods" might be more useful to call this "pharmacological and nonpharmacological methods" since nonpharmacological methods may include systems which do not fit well under "counseling methods" (e.g., behavioral, alarm reminder systems).	Thank you. We have changed this sentence as is suggested.
TEP #5	Executive Summary-Discussion	Due to the methodologically-rigorous manner in which these 11 studies were chosen for this CER, several innovative adherence cohort studies were not illuminated. However, given that this CER has the potential to drive future research directions in HCV adherence, it might be useful to point researchers towards some cohort studies which described interesting features of interventions that may warrant further testing in RCTs. These might include: Grebely et al EJGH, 2010; Groessl et al, JVH, 2011; Ho AJG, 2008; Zanini et al Clin Ther 2010; Aurora et al, NEJM, 2011 Project ECHO; and the NIDDK-funded Virahep-C study (see Conjeevaram 2006 Gastro and the study protocol online at https://www.niddkrepository.org/niddkdocs/VIRAHEPC/protocol/VirahepC_Protocol.pdf with description of Adherence and Education Program on pages 15-17).	We reviewed all of the references that were sent by this reviewer. These studies were all screened or reviewed in full-text in our original review and were excluded based on *a priori* eligibility criteria. Section 5 of the Virahep-C protocol described a prospective cohort study that specifically examined the relationship between adherence and treatment response. This study did not examine the association between an intervention and treatment outcomes (our question of interest). Additionally, it appears that all the patients in this cohort will receive an Education Program (i.e., no control). Thus, it is ineligible for our review according to the eligibility criteria.
TEP #6	Executive Summary	The Executive Summary can be shortened.	Given the significant complexity and heterogeneity of studies, we believe the ES provides a reasonable level of detail about adherence interventions, patients, and outcomes. We feel that in shortening the ES we would lose important information.
TEP #5	Abstract	Page 6, line 55: Given the significance of the problem, it would be useful if the authors highlighted the multiple definitions of adherence in the Abstract Conclusions section in order to encourage researchers to come to a consensus on terminology.	We add a line to the very last sentence of the abstract that calls for adopting a standard definition of adherence.
TEP #1	Introduction	Authors do a good job setting up the general context of Hep C and therapy, then moving on to rationale for the review. Concise yet thorough.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Introduction	In the content section - Introduction breakdown is titled differently in the executive summary.	The current guidance for the ES of AHRQ reports has fewer headings. The headings of the full report are not mirrored in the ES.
TEP #3	Introduction	Comprehensive and well written introduction. One detail that could be helpful for readers is the description of the (health) professional needed to deliver any of the 5 types of interventions or parts of it (e.g. physician, nurse, pharmacist etc)	We added a sentence at the end of the paragraph after Table 2 that discusses the types of providers who might administer these interventions.
TEP #4	Introduction	The introduction is well written. No comments or suggestions.	Thank you. No response necessary.
TEP #5	Introduction	Page 33, line 14: Might cite Mchutchison's adherence paper and conjeevaram et al 2006 Gastro.	Thank you for this suggestion. These citations were added.
TEP #5	Introduction	Page 33, line 52, Table 1: please look at 2 studies by Fasiha Kanwal in the VAMC system. She studied center and provider characteristics as predictors of treatment outcomes. Did they explore outcomes such as SVR?	We reviewed the article by Kanwal titled "Predictors of Treatment in Patients with Chronic Hepatitis C Infection—Role of Patient Versus Nonpatient Factors". In this article, the authors examined what facility-, provider-, and patient-level factors were associated with being evaluated and/or treated for HCV. They did not examine how these factors relate to treatment response (e.g., SVR) or patient adherence. Therefore, we do not feel it was appropriate to add this reference to Table 1. We were unable to identify the other article by this author.
TEP #5	Introduction	Page 34, line 27, Table 1: Cite Evon et al 2011 Social Support paper, which found no relationship with SVR or adherence.	Thank you for this recommendation. We have added this citation to Table 1 and have changed the relationship between socioeconomic status/social supports and adherence to say "Mixed".
TEP #5	Introduction	The authors might want to keep an eye out for Evon et al's paper (Under Review), "Adherence during PEG/ribavirin regimens for chronic hepatitis C" where we found demographics, SES variables, and symptoms predictive of missed doses and treatment persistence.	This paper has not been published. We are happy to review this paper if it is published before our report is finalized.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Introduction	Page 34, line 36 to page 35, line 37: This section provides a good explanation and is very salient to clinicians' interpretation of adherence studies and how research might move the field of adherence to HCV treatment regimens forward.	Thank you for this comment. No response necessary.
TEP #5	Introduction	Page 35, line 13: "missed doses by decision": Patients miss doses for other reasons such as simply forgetting and getting busy with their routine.	We changed this text slightly.
TEP #5	Introduction	Excellent, well-articulated sections on adherence definitions, risk factors, association with SVR.	Thank you. No response necessary.
TEP #5	Introduction	Page 36, line 34-43: Conjeevaram et al 2006 Gastro, found adherence to be one of a few independent predictors of SVR in multivariate analyses.	We added this citation. However, this didn't change our statement that the association between adherence and SVR is inconsistent.
TEP #5	Introduction	Page 37, line 16: Do the authors specifically mean "medication adherence"? Or is the intention to use a more inclusive global terms (i.e. treatment adherence or patient adherence)?	We changed the report to refer to "patient adherence" or "adherence" more generally throughout the report to reflect both medication and medical plan adherence on behalf of the patient.
TEP #5	Introduction	Page 37, lines 7-49: "interventions for improving adherence": Consider merging adverse side effect management interventions into patient-level interventions and subdivide further into nonpharmacological and pharmacological interventions. I would keep examples of psychological treatments (e.g., CBT, coping skills training) separate from more generic "counseling" which can be performed by many providers.	We developed the categories according to the underlying mechanisms of action. We agree that interventions for managing adverse events may be considered patient-level interventions. However, adverse events of medications represent an important and independent domain for patient non-adherence in hepatitis C treatment. Thus, we consider it reasonable and important to separate these interventions from other patient-level interventions. We also chose to group all behavioral interventions ("psychological treatments" and "counseling") together.
TEP #5	Introduction	Page 38, line 33: Again, be consistent with use of terms. The authors previously used the term "medical adherence" for what I think they intend here instead of "treatment plan adherence."	We have made revisions throughout the report to make the term consistent.
PR #1	Introduction	The Introduction was very well written and provided a sufficient overview of the epidemiology, natural history, treatment of HCV infection, and HCV treatment adherence.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
PR #1	Introduction	Table 1, which present factors associated with SVR and adherence to HCV therapy, is accurate, very well referenced, and quite clear. This is an important figure because any intervention must be built on a conceptual model of the barriers to HCV therapy. As such, this Table connects quite nicely to Table 2.	Thank you. No response necessary.
PR #1	Introduction	The authors might want to consider including insulin resistance as a comorbid medical condition associated with SVR, as several studies and a meta-analysis (see Eslam et al. Aliment Pharmacol Ther 2011; 34: 297–305) have demonstrated this. Additionally, as is pointed out later in the section titled "Adherence in the Context of Chronic HCV Treatment," PEG-IFN and ribavirin adherence are also factors associated with SVR, and the authors might want to consider including this as a patient-related factor	We added the Eslam reference to Table 1 under patient-related medical comorbidities. In table 1, we aimed to articulate factors that affect treatment response and adherence. As adherence is the factor of our primary interest in relation to SVR it was not included in the table. We had detailed descriptions regarding the association between adherence and SVR in the section "Association of Adherence with Sustained Viral Response"
PR #1	Introduction	The key questions are appropriate and clearly stated. They are clinically relevant, and highlight the need for research in final health outcomes, particularly clinical liver events, mortality, and quality of life (page 8 of the Introduction, line 28: transmission of HCV as an outcome will be extremely difficult to evaluate in any study design).	Thank you. No response necessary.
PR #2	Introduction	Well written with a clear rationale.	No response necessary.

Commentator & Affiliation	Section	Comment	Response
PR #3	Introduction	The introduction is thorough and well-written, limited however by the rapid changes in the therapeutic paradigm that are evolving as experience with PEG, ribavirin and DAAs grows. The authors may wish to update the section on "Treatment of Chronic Hepatitis C Infection" and Table 1 in that section. In this section as well, it would be useful to discuss in more detail the methodologies used to collect adherence data (Page 5, lines 32-36).	We included the discussion about changes in the treatment paradigm, particularly the introduction of new protease inhibitors to the treatment of genotype 1 HCV infection, in the "Treatment of Chronic Hepatitis C Infection" section of the report. Table 1 documents the risk factors that had been reported up to the time of our search. Including more details about methods for collecting adherence data can make the introduction lengthy and less focused. In particular, a number of existing studies have discussed in detail the methods for collecting adherence data, and we cited those studies in the introduction. Interested readers may find those references helpful.
PR #3	Introduction	Adherence is a complex, time-oriented activity by patients, and defining adherence by a single term or number is often not informative. A recent publication that may not have been available to the authors at the time of this review is an article on adherence taxonomy by Vrijens et al. (Vrijens B, De Geest S, Hughes DA et al. for the ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012 May; 73(5): 691-705). Studies using electronic monitoring, while not applicable in all settings, have shown that premature discontinuation (non-persistence) is more important than poor implementation or execution of a dosing regimen in lack of efficacy. Unfortunately, most published literature, including those evaluated in this review, do not provide specific details of the nature of patients' adherence and there is a lack of uniformity in the terminology used to describe deviations from prescribed therapies. Given the importance of this review in stimulating new research, this issue deserves more attention so that it can improve the conduct, analysis and interpretation of scientific studies of medication adherence.	Thank you for this comment. We included a paragraph in the Research Gaps section of the discussion discussing the definition of adherence, and highlighted the needs for standardizing the use of adherence terms and clearly defining adherence in the hepatitis C adherence studies. We added the citations suggested by the reviewer.

Commentator & Affiliation	Section	Comment	Response
PR #4	Introduction	Page 33 - line 4. In the context of DAAs (and specifically telaprevir), undetectable viral load at 4 and 12 weeks is considered an extended rapid viral response (eRVR). There is no mention of the role of IL28B gene and its role in predicting response to treatment. With DAAs, T/T vs. C/C genotype is associated with a decreased rate of SVR.	We changed the term to extended rapid viral response. We added the genetic variation in IL28B to the list of factors affecting treatment response in Table 1.
PR #4	Introduction	A distinction should be made between frequent drug use (daily or every other day) vs. less frequent drug use. Not all drug use is associated with decreased rates of SVR.	We agree that the frequency of drug use might be associated with SVR. However, we did not identify a study that demonstrated the association, and were not able to include this in the Table 1.
PR #4	Introduction	Nice discussion of the differences among physician-led dose reductions, treatment discontinuation, and adherence.	Thank you. No response necessary.
TEP #6	Introduction	The introduction discusses variables that may affect viral response and adherence to HCV treatment and summarizes this in Table 1. This is an area of research with a vastly larger number of high quality studies than the literature on studies of adherence interventions to HCV treatment. However, only a very cursory and selective review of this literature is provided in the Introduction. This stands in marked contrast to the highly rigorous approach taken to analyzing the much less developed literature on adherence interventions. A more rigorous and systematic approach to analyzing the literature on predictors of viral response and adherence is warranted.	Table 1 aims to provide a general summary of potential risk factors associated with treatment response and adherence that facilitates the understanding of the potential confounding factors for the association between the adherence interventions and treatment outcomes specifically for hepatitis C. Because this was not a key question of this systematic review, we did not aim to systematically review the literature regarding this topic. Nonetheless, we included good-quality and representative studies addressing these issues.
TEP #1	Methods	Search strategies are stated, logical and reproducible. Inclusion and exclusion criteria seem reasonable. Definitions are acceptable but I don't think it's reasonable to expect long-term outcomes from these kinds of studies. That would take 5-10 yrs and millions of dollars.	We have revised our future research recommendation to reduce the emphasis on long-term outcomes in the discussion of the report, and suggested the need for confirming the effect on intermediate outcomes.
TEP #2	Methods	Inclusion and exclusion criteria satisfactory.	Thank you. No response necessary.
TEP #3	Methods	I found the methods to be adequate and described with enough detail	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Methods	Inclusion and exclusion criteria look appropriate. The search strategy looks reasonable and logical. The flow diagram makes sense. The outcomes are appropriate given the condition. Methods for quality appraisal and qualitative synthesis are clear	Thank you. No response necessary.
TEP #5	Methods	Page 41, line 40-41: Might use the term "treatment persistence" instead of "treatment duration" as this is a more commonly used term in the broader adherence literature (See Cramer et al, Medication compliance and persistence: terminology and definitions. Value Health 2008).	Thanks for the suggestion. To make the term consistent within our report, we opted to use the term treatment duration.
PR #1	Methods	The authors clearly state their search strategies, and these are logical. The inclusion and exclusion criteria are appropriate and justifiable. The definitions or diagnostic criteria for the outcome measures are appropriate. The statistical methods used are appropriate, including the individual assessment of study quality. Given the methodological heterogeneity of the studies included, it would not be appropriate to conduct a pooled analysis, as the authors state on page 13 of the Methods, line 10.	Thank you. No response necessary.
PR #2	Methods	Is it possible that studies were missed due to the search date restrictions. That is, even though pegIFN-alpha was approved in 2001, it is likely that clinical trials were published before this date. As HCV infections are not my area of enterprise this comment may be misplaced. But, clinical trials were certainly completed before FDA approval which means it was likely that some published/unpublished data exist before this point.	It is possible that trials testing the efficacy of pegIFN-alpha were published before2001. However, given that our aim was to evaluate the effect of adherence interventions on adherence and treatment outcomes, these were excluded according to our eligibility criteria.
PR #2	Methods	Inclusion criteria appear appropriate	Thank you. No response necessary.
PR #2	Methods	The study quality assessment appears appropriate with the exception of the rating system of good, fair and poor. Performing such global ratings for each study causes a specific loss of information on where the flaws lie. But, in fact, the explorations of reasons for heterogeneity is where risk of bias information should be used. For example in subgroup analyses. But, the authors performed a qualitative systematic reviews were by using the AHRQ methods, which is appropriate due to the between study differences	We followed a standard EPC systematic review approach to assessing the risk of bias (i.e., quality of studies). We reported information about each component associated with risk of bias (e.g., allocation concealment) and the overall assessment. Appendices D and E list study-specific risk of bias concerns. We agree that it was impossible to conduct any quantitative analysis given the differences in studies and data.

Commentator & Affiliation	Section	Comment	Response
PR #3	Methods	This is well-described and executed, and limitations of the 11 individual papers that were utilized in the final analysis are carefully pointed out.	Thank you. No response necessary.
PR #4	Methods	The inclusion and exclusion criteria are well-justified. The definitions of outcome measures are appropriate, and the rigorously grading system is clear	Thank you. No response necessary.
TEP #6	Methods	The methods are clearly stated and appropriate.	Thank you. No response necessary.
TEP #1	Results	Amount of detail got to be tedious and repetitive. Tables do a good job summarizing the review.	We are glad that the tables adequately summarize the review. We provided more details in the narrative section in order to be comprehensive.
TEP #2	Results	Characteristics of the study are clearly described - somewhat lengthy.	While we agree that the study characteristics are somewhat long, we believe they are appropriate and necessary given the high level of heterogeneity in the body of evidence. We feel that the important variations in patient and intervention characteristics need to be clearly captured in the report.
TEP #3	Results	The results are summarized concisely. In particular, there is a good level of detail in the main body of the report. As mentioned previously, there could be some more details about the interventions in the executive summary. The readers will appreciate the details given on the eligibility criteria of study participants.	This is a good suggestion. We added Table 6 from the full report to the Executive Summary (now Table A).
TEP #4	Results	Given the complexity and heterogeneity of the interventions, the detail in the narrative seems about right. One suggestion would be to reframe the outcomes discussed in the results through the KQ for each level of intervention. For example, After you discuss the various studies and move to describing the 'outcomes' it might be helpful to have a section heading such as 'Final Health Outcomes' then discuss what was found, move next to 'viral outcomes', and finally 'Adherence' .	We believe we organized the outcomes sections as suggested. For each level of interventions, we first reported health outcomes including quality of life. We then reported virological response, followed by adherence outcomes.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 48, Table 6: This is a very important table summarizing the 11 studies. Under column "outcomes measured" authors use the generic term "adherence." Since adherence is the key outcome of adherence interventions and it has so many different facets, it would be more informative to use more precise terms, as the authors suggest on page 41, lines 40-41. They could indicate medication vs. protocol adherence, or as on page 41, what was measured: frequency, dosage, treatment duration, or timing? The term "adherence" here is not precise enough. All other outcomes measured are self-explanatory.	The purpose of Table 6 was to give an overview of the evidence body. The column "outcome measured" aimed to inform readers what domains of outcomes a study investigated. We included the details about the measurement and definition of adherence in the outcome tables (Table 8-11).
PR #1	Results	The amount of detail presented in the results section is completely appropriate. The authors present the results of their search strategy, and report the excluded studies and reasons. The characteristics of the studies and grading of the strength of evidence is clearly described and well reported in Table 6. The other accompanying Tables are clear and appropriate. I do not believe that the investigators overlooked any studies that ought to have been included or included studies that should have been excluded. The results are presented fairly and highlight many of the deficiencies in this area.	Thank you. No response necessary.
National Viral Hepatitis Roundtable	Results	The NVHR supports the report's conclusion that the strength of the current evidence is low and that more adequately powered and rigorously conducted RCTs are needed to test HCV adherence interventions on intermediate and health outcomes, as well as in genotype-1 patients receiving a triple therapy. We are especially pleased that AHRQ highlights the limitations of cohort studies, including their susceptibility to selection bias and challenges accounting for unknown prognostic factors, versus the more optimal randomized controlled trial (RCT). At the same time, we appreciate AHRQ's recognition of instances in which cohort studies may prove more valuable than RCTs, including the collection of longer-term outcomes data, such as cirrhosis and hepatocellular carcinoma, through patient registries.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
National Viral Hepatitis Roundtable	Results	While the identification of gaps in current research helps point to areas of future investment, it also signifies the large amount of work that still needs to be done in this field and the continuing lack of conclusive evidence regarding best practices. Therefore, we caution the public and private sector against using this report or the data it contains for payment decisions. All too often in healthcare we see inappropriate interpretations and applications of weak evidence. For example, data on specific hepatitis screening strategies remains spotty and inconclusive, yet is often relied on by insurance companies, which limits our ability to identify patients in need of treatment and to control infection rates.	Thank you. No response necessary.
PR #2	Results	Literature search results are well described -studies are well described -As far as I can tell, the results are completely described, and are appropriately categorized	No response necessary.
PR #4	Results	There is a great degree of detail in the tables which is excellent. I am unaware of any studies that should have been included or studies that were excluded.	Thank you. No response necessary.
PR #4	Results	It would be nice if the actual studies were referenced in the key points sections.	We can see the benefit of doing this. However, we opted to keep the key points succinct and only included the references in the results text.

Commentator & Affiliation	Section	Comment	Response
TEP #6	Results	The studies that fall in the Adverse effect management interventions are problematic. While these can be construed as adherence interventions given that adherence is often defined as persistence in HCV therapy, the primary goal of these interventions is not focused on patient adherence but is a part of the clinical management of treatment. If studies of adverse effect management are included then this list is far from complete. There are numerous studies which have examined ribavirin dose reduction and the impact on outcomes (Reddy KR et al. Clin Gastro Hep 2007 to name one). This would also open the door to including studies which have examined outcomes with interferon alfa-2a vs. 2b, fatigue management, rash management, etc.	We agree that this is a complex issue and that adverse event management is largely considered part of clinical management. In this systematic review, we included four studies that clearly described the adverse event management as a mechanism to help improve patient adherence outcomes and/or reported adherence outcomes (e.g., treatment-related depression). These types of interventions—which often aim to reduce symptomatic adverse events—can improve patients' use of medications, and represent an important approach to enhancing patient adherence to treatment. We added the above discussion to the full report.
TEP #6	Results	In Table 6, when Adherence is cited as the Outcome Measure it should be specified what this refers to as this varies across studies.	We included this level of detail in the outcomes tables (Tables 8-11). Table 6 was meant to simply capture what broad-level outcomes were measured.
TEP #1	Discussion	Line 44-5 on p 15 doesn't make sense. As stated above, it's unrealistic to expect researchers to track long term outcomes without adequate funding. I agree that a standard definition on adherence is needed.	Thank you for this comment. We have revised our recommendations regarding long-term outcomes.
TEP #2	Discussion	Applicability in the era of DAA agents needs to more emphasized. Expand how increased pill burden with DAA agents will effect adherence.	We discussed the limited application of current findings to patients receiving protease inhibitors in addition to the standard dual therapy in the limitation section. We also discussed how the increased pill burden may affect adherence in the future research section. We think this level of detail should be adequate in the discussion of the impact of protease inhibitors on adherence.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion	I am a methods expert and cannot say much about the need from a clinical perspective. The call for better studies and some standardization (e.g. outcome measurements) seems very appropriate.	Thank you. No response necessary.
TEP #4	Discussion	The discussion is well crafted. It highlights the major findings and discusses the extensive list of limitations and holes in the evidence. I am not aware of any missing literature, although this is not my content area.	Thank you. No response necessary.
TEP #4	Discussion	The discussion describes some important areas for that future research needs to focus. Using more rigorous designs with more uniform definitions of adherence. Given that SVR is considered an acceptable surrogate for new drug approval, it will also likely suffice for interventions to improve adherence.	Thank you. No response necessary.
TEP #4	Discussion	The conclusions well supported and are generally supportive of several interventions that seem to be effective at improving adherence and perhaps SVR in some cases.	Thank you. No response necessary.
TEP #5	Discussion	Page 80, line 53: important point made about the intensity, length and the parties who are trained to deliver interventions. This information will inform the feasibility of disseminating efficacious interventions in real-world settings.	Thank you. No response necessary.
TEP #5	Discussion	Page 81, line 14-18: This is a very good point, perhaps worth highlighting in the ES. Until researchers come to consensus on the different facets of adherence, this will continue to be a major obstacle.	The ES included this as a research gap.
TEP #5	Discussion	Page 81, lines 40-48: It might be useful to state that while this is a noted limitation, future research should focus on relationship with adherent behaviors and SVR first.	We added a sentence expressing the need for future research addressing the relationship between adherence and SVR, including the effects of adherence interventions in achieving SVR.
TEP #5	Discussion	Page 82, line 52: The authors might use the term “behavioral or psychological treatments” rather than the generic term of “counseling” methods. Improving adherent behaviors and patients’ tolerance of side effects will likely require specialized treatments and not simply supportive “listening” counseling, as this term seems to imply.	We agree with suggestion and have changed it to read “behavioral interventions”.
TEP #5	Discussion	Page 83, line 22; Good point to use pre-existing registries	Thank you. No response necessary.
TEP #5	Discussion	Page 83, 40-44: Good point that 80/80/80 is arbitrary and researchers should seek to identify more precise cut-offs for each medication and duration of treatment.	Thank you. No response necessary.
TEP #5	Discussion	Page 83, lines 46-53: Nice description of each deviation from the protocol and why they need to be measured separately.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Discussion	Page 84, lines 6-19: Point well-taken, however due to page restrictions of most manuscripts, authors often do not have space to dedicate to these details. The authors might suggest that researchers (and journal editors) publish methods paper describing intervention development, components, intensity, training of the interventionist, etc, so that these details are well-documented prior to publishing the main paper.	We appreciate the suggestion, and have incorporated it into the full report.
PR #1	Discussion	The results and implications of the major findings are clearly stated in the Discussion. The authors adequately explain the limitations of the individual studies throughout the results, and summarize these quite well in the Discussion. The review's limitations are also well stated. No important literature or key facts were excluded. The section titled "Applicability of the Evidence to the U.S. Health Care System" is excellent and highlights the need for new research given the recent release of direct-acting antivirals. The future research section clearly delineates areas of major research need (e.g., adequately powered RCTs, appropriate standardized methods to measure HCV treatment adherence, evaluation of important outcomes, accounting for dosage reduction/discontinuation).	Thank you. No response necessary.
PR #1	Discussion	The section titled "Evidence Gaps" (lines 46-53) suggests that the most effective interventions would include a combination of changes made to the systems and settings in which HCV care is received, the packaging and delivery of medications, support and education, and management of treatment-related side effects. My concern with this suggestion is that I am not sure it would be feasible to create a single comprehensive intervention that would address all of these issues. I think that separate randomized trials would likely have to address system-level and regimen-related interventions whereas patient-level and adverse effect management interventions could be more feasibly combined in a single intervention and evaluated. For the latter interventions, tailoring problem-solving solutions to an individual's patient-level and adverse effect-related adherence barriers and monitoring adherence in order to give feedback is the type of flexible multi-component intervention that holds promise. This approach has been shown to improve adherence in randomized, controlled trials evaluating managed problem solving for adherence to antiretroviral therapy for HIV infection.	We agree that a study that tests a comprehensive intervention involving multiple components may be challenging to implement. However, we disagree with the reviewer that this is not feasible in general. Several interventions for other health behaviors have been designed and conducted that address factors at multiple levels of influence (e.g., targeting patient- and system-level factors). We feel strongly that these types of interventions would be an important contribution to the field of HCV treatment adherence.

Commentator & Affiliation	Section	Comment	Response
National Viral Hepatitis Roundtable	Discussion	While it is unfortunate that the current set of available data on this topic is poor and of limited focus, we are grateful that AHRQ calls attention to the need for additional investments in high quality research on this topic by pointing out gaps in the evidence. Just about every clinical trial currently has a component that evaluates adherence, yet adherence is rarely, if ever the primary focus of these studies. We call on the healthcare community as a whole, including larger health systems and public and private payers, to invest in this work. In fact, we view research on adherence to HCV treatment interventions as an ideal priority for funding under the newly created Patient-Centered Outcomes Research Institute (PCORI).	Thank you. No response necessary.
PR #2	Discussion	Main findings are clearly stated. Table 12 is an excellent overview of the level of evidence for each key question by group -applicability is clearly discussed. The evidence gaps and future research sections are well organized and appear to cover most areas	Thank you. No response necessary.
PR #2	Discussion	Limitation of their approach does not seem to be complete: I would be sure to discuss the problem of the search cut-off date, the problems of a qualitative approach, potential issues with the risk of bias assessment. See previous comment in Methods.	We followed a standard EPC systematic review approach to assessing the risk of bias (i.e., quality of studies). We reported information about each component associated with risk of bias (e.g., allocation concealment) and the overall assessment. Appendices D and E list study-specific risk of bias concerns. We agree that it was impossible to conduct any quantitative analysis given the differences in studies and data. Regarding the search cut-off date, it is possible that trials testing the efficacy of pegIFN-alpha were published before2001. However, given that our aim was to evaluate the effect of adherence interventions on adherence and treatment outcomes, these were excluded according to our eligibility criteria.

Commentator & Affiliation	Section	Comment	Response
PR #3	Discussion	See my previous comments regarding the limitations of the prior studies and on the design and implementation of future research on interventions to improve adherence. It has been said "You can't manage what you can't measure" and this is particularly applicable to interventions for improving adherence.	We included a paragraph in the Research Gaps section of the discussion discussing the definition of adherence, and highlighted the needs for standardizing the use of adherence terms and clearly defining adherence in the hepatitis C adherence studies. We added the citations suggested by the reviewer.
PR #3	Results	Given the final conclusions that "Adherence interventions might improve patient adherence and virological response in patients with chronic hepatitis C, [however] the strength of evidence is low...More adequately powered and rigorously conducted RCTs are needed to test HCV adherence interventions both on intermediate and health outcomes." This reviewer would add that evaluating the effectiveness of interventions to improve adherence require better approaches to measuring adherence, which is a very critical limitation of almost all studies thus far.	Thank you for this suggestion. We included this as a limitation of existing studies in the discussion.
PR #4	Discussion	The overview was nicely done. I agree with the conclusion that the evidence for increased SVR was most consistent for patient-level adherence interventions. The conclusion section does a nice job in reinforcing highlights in both health outcomes and intermediate outcomes (system-level, regimen-related, patient-level, and adverse effect management interventions). The sections on applicability of the evidence to the United States, clinical implications, evidence gaps, and future research were all well-done.	Thank you. No response necessary.
TEP #6	Discussion	It would be helpful to frame these findings in the context of the evidence base for adherence to other medical treatments. Is this paucity of evidence for adherence interventions in HCV treatment similar to the state of the literature for other medical treatments or does it stand out in some way and if so, why?	Although making a comparison between the adherence literature in HCV versus other disease conditions would be helpful, this analysis is beyond the scope of this review. In particular, it is probably difficult to explain the reasons for the differences, without carefully reviewing the literature for other disease conditions.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Appendix	Page 99, Appendix B: The authors may be interested in Evon et al's adherence paper when published which highlights risk factors for missed doses and persistence.	We were unable to locate this specific paper to evaluate for its relevance as a "study pending assessment" to list in Appendix B.
TEP #5	Appendix	Page 101: The title of Appendix is "Excluded Studies" however, some, if not all, of the 11 studies included in the review (Larrey, Ramsey, etc) are listed in this Table.	Some our included studies were included for one KQ, but excluded for another, which is why they were included in this appendix. The excluded studies list, however, has been updated to only include studies that were excluded in our review.
TEP #1	General	Report is well structured; organized and main points are clearly presented. It's completely useless to the practicing clinician, however. Perhaps it can be used to influence policy and funding decisions. Key questions are explicitly stated. The target population and audience are defined. However, as a clinician who treats HCV patients and interested in improving adherence, this was not a helpful document. It basically says that the literature in the area is flawed and there is no evidence to make any recommendations. I want to know what works; weren't there a few studies of good enough quality that showed an effect? If so, can those best practices be expounded upon? It otherwise reads as a very long-winded bashing of the literature. As a researcher, I think it is unreasonable to expect that adherence studies are going to be able to track some of the primary (and long-term) outcomes like mortality. That is a very expensive study.	This body of literature is very heterogeneous, the quality of evidence is generally poor, and the study sample sizes are also small. We agree that the findings are probably very limited for clinical practice. In our study, we identified 5 good or fair studies, 4 of which were cohort studies, and one is a fair quality RCT. None of those studies suggested that adherence interventions substantially improved virological response. Three studies suggested adherence was improved, whereas the other two showed lower adherence level associated with the intervention. Given the inconsistency of the findings, the lack of evidence showing improved clinical outcomes, and the fact that the findings are largely based on observational studies, we are uncomfortable recommending any specific intervention at this stage. However, we did expand the "Implications for Clinical Decisionmaking" section. (Response continued on next page)

Commentator & Affiliation	Section	Comment	Response
			Our review reveals that there is significant research gap in the improving adherence of chronic hepatitis C treatment, and calls for studies that use rigorous research methods to examine interventions for improving adherence in chronic hepatitis C. Additionally, our review suggests some interventions (e.g. patient-level interventions) may be effective. We agree that long-term studies may not be feasible due to the substantial cost of running such studies. We have revised the recommendation from our report.
TEP #2	General	Excellent thorough paper. Very detailed. Somewhat lengthy.	We agree this is a long report. We hoped to strike a balance between our thoroughness and detailed descriptions of the study characteristics and results while being concise. We hope that the full report provides such detail and the Executive Summary provides a more succinct version of the full report.
TEP #2	General	Usability is somewhat limited as HCV therapy is rapidly evolving - especially as IFN free therapy will be the standard of care in 3-5 years	We agree. We pointed out in the discussion that, with the introduction of new protease inhibitors, the current studies may be limited in the applicability to a more complex treatment regimen.
TEP #3	General	The systematic review is well planned and conducted. The report is well written. The only criticism is that the abstract and executive summary do not say much about the content of the interventions. The interventions were heterogenuous and it requires some space to describe them but for a clinical audience there could at least be some details about the content of the interventions	We have now included Table 6 in the full report as Table A in the Executive Summary to provide this information.

Commentator & Affiliation	Section	Comment	Response
TEP #3	General	The report is well written and organized. It is always challenging to summarize results non-quantitatively but the authors did a good job.	Thank you. No response necessary.
TEP #4	General	The issue of adherence is a critical challenge for achieving outcomes in patients. The report highlights the specific challenges in patients with HCV infection. The target population is appropriate and clear. Given the condition, the key questions seem appropriate.	Thank you. No response necessary.
TEP #4	General	The report is well structured and easy to follow. My one suggestion above would mainly help orient the reader to the different sections of each domain of interventions. That is, the first part is more descriptive of the intervention and details of the study design. The second part describes what was found.	We believe we organized the results of full reports as TEP #4 suggested.
TEP #5	General	The target population and audience are explicitly defined, and the key questions are appropriate and explicitly stated. As the authors point out, this CER is based on studies of dual therapy, not the most current "triple therapy" HCV regimens that commenced in 2011. As a result, the clinical meaningfulness of this review is attenuated. Nonetheless, we can anticipate that adherence will be an even greater challenge during triple therapy regimens given the complex dosing schedule and additional side effects. Therefore this CER highlights the significant gaps in HCV adherence research and may stimulate research at multiple levels of change.	Thank you. No response necessary.
TEP #5	General	Overall, the authors should be commended on a CER that is well-written, organized, and concise. The CER will make a significant contribution to the field of HCV, most notably, through highlighting the dearth of evidence in this area and stimulating the development of adherence interventions to be tested in methodologically-rigorous RCTs. It offers key stakeholders a comprehensive state of the current knowledge with regard to the efficacy of various adherence interventions during dual interferon and ribavirin (IFN/RBV) therapy. The two most salient take home messages from this CER are (1) the evidence on intervention efficacy is insufficient at this time and high quality RCTs and observational studies with comparator groups are needed; and (2) a common consensus on definitions and the lexicon to be used in HCV adherence is needed to facilitate comparisons among studies and interpretation of findings.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP #5	General	The three primary recommendations are to: 1) revise the 5 intervention level system; 2) provide a global adherence term that is defined early in the executive summary and applied consistently throughout the paper; and 3) reduce the emphasis on long-term final health outcomes and focus future research on high quality studies that evaluate the association between interventions and adherent behaviors and SVR as the primary outcomes.	Re comment 1: The reviewer proposed to classify the patient-level interventions by pharmacological versus non-pharmacological strategies. Although this may represent an alternative classification approach, we don't find this method is superior to our current classification or improves readability. We developed the categories according to the underlying mechanisms of action. We agree that interventions for managing adverse events may be considered patient-level interventions. However, adverse events of medications represent an important and independent domain for patient non-adherence in hepatitis C treatment. Thus, we consider it reasonable and important to separate these interventions from other patient-level interventions. (more response in the next page)

Commentator & Affiliation	Section	Comment	Response
			We agree on the possibility of further dividing the patient-level interventions into finer categories (e.g. educational, supportive, etc). However, given the paucity of evidence about patient-level adherence interventions and the lack of detail regarding each intervention, we did not further categorize the interventions. Re comment 2: We have changed the text to clarify that our definition of "adherence" (now termed patient adherence or "adherence" more generally) refers to both adherence to one's medication and adherence to the full medical plan. Re comment 3: we reduced the emphasis on long-term health outcomes, and suggested the need for confirming the effect on intermediate outcomes in the Research Gaps section.

Commentator & Affiliation	Section	Comment	Response
PR #1	General	This is an outstanding Comparative Effectiveness Review. The report is well written and very clear. The study methods are rigorous and well described. The results are clear and adequately supported by the accompanying Figures and Tables. The report is clinically meaningful and will be useful to the clinicians, researchers, patients, and other stakeholders of hepatitis C care and treatment. The target population is explicitly defined. The key questions are appropriate and clearly stated. Overall, the methods used to review and select the articles are quite clear. The report is very well referenced. It provides a sufficient overview of the hepatitis C virus epidemiology, natural history, and antiviral treatment before focusing on studies of HCV treatment adherence and HCV treatment adherence interventions. It clearly discusses the strengths and limitations of each of the selected studies, synthesizes the results, discusses potential review limitations, and highlights the areas of future research. This will be a very valuable report to all in the hepatitis C field.	Thank you. No response necessary.
PR #1	General	This is an outstanding report. It is clearly structured and well written. The conclusions can certainly be used to inform future research and funding needs (which are great in the area) and policy decisions.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
Abbott Laboratories	General	Abbott commends the Agency for Healthcare Research and Quality (AHRQ) for conducting this comparative effectiveness review on adherence to Hepatitis C virus (HCV) treatment interventions. While effective detection and therapies are critical for the treatment of chronic HCV infection, treatment adherence is also a critical component of the treatment paradigm. It is important to understand the many factors that might contribute to patients not taking prescribed medications as well as the potential impact of adherence interventions on health outcomes. As detailed in the draft review, there are many evidence gaps related to the impact of HCV treatment adherence interventions on health outcomes and adherence. Clearly, more research is needed in this area. We encourage AHRQ to work with its partners and stakeholders to pursue targeted research in the identified gaps. Abbott also notes that AHRQ's findings from its broader research review on the comparative effectiveness of medication adherence interventions could complement this review on HCV treatment adherence.	Thank you. No response necessary.
National Viral Hepatitis Roundtable	General	The NVHR appreciates that the report sets out to gather data on both the intermediate and final health outcomes related to antiviral therapy treatment adherence interventions. The NVHR finds great value in studies that evaluate final health-related outcomes—such as HCV-morbidity, mortality, and quality of life—and we support follow-up periods that account for longer-term health outcomes. We also recognize the benefit of studying intermediate outcomes. The FDA's recent approval of protease inhibitors to treat chronic HCV infection, as well as future regimens currently under development, make issues such as sustained viral response, resistance, and side effects increasingly important. The NVHR welcomes AHRQ's attention to these issues.	Thank you. No response necessary.
PR #2	General	The proposal is very well written and organized in a clear manner. This proposal asks an important question. This review identifies significant gaps in this literature and can help direct funding for future research.	Thank you. No response necessary.
PR #2	General	The report was well structured, the points were clear, and this report can help guide funding allocation to projects that address the gaps identified in the literature.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
PR #3	General	The underlying rationale for this review is based on "The existing body of literature [which] consistently shows that increasing adherence to dual therapy is associated with improved likelihood of achieving SVR. As such, efforts to improve treatment adherence in hepatitis C are needed." Three references for this statement using PEG and ribavirin are cited, although more recent data from studies using direct acting antiviral agents (DAAs) support this assumption.	We included discussion that the introduction of protease inhibitors to the standard treatment may influence the adherence and the effects of adherence interventions. We suggested in the discussion that future studies should address the effects of adherence interventions in patients using protease inhibitors.
PR #3	General	Although the results of the literature review found that the strength of evidence for the value of interventions was "insufficient" to show value for improving any of the three final health outcomes, this itself is an important finding and supports the conclusion that "more adequately powered and rigorously conducted RCTs are needed to test HCV adherence interventions." In the period since the literature review was ended, this reviewer is aware of several ongoing efforts in the pharmaceutical industry and in some clinical practices to measure and in some cases try to improve adherence. These efforts are, as yet, unpublished. I believe that this report will stimulate additional, better-designed studies regarding the most cost-effective interventions aimed at improving adherence in this important therapeutic area.	Thank you. No response necessary.
PR #3	General	I think the key questions and the target population (patients with HCV) are well defined. The target audience (physicians, gastroenterologists and clinics specializing in the management of HCV-infected patients) is also appropriate, though another target audience that is not as well defined are those scientists and clinical investigators involved in the development of DAAs.	This review provided a comprehensive review of existing evidence about adherence interventions for chronic hepatitis C, and clearly pointed out methodological limitations of existing studies and research gaps. We believe this provides important information for researchers.
PR #4	General	This is an excellent report that sums up the current level of evidence regarding the effectiveness of hepatitis C treatment adherence interventions. It lays the groundwork for future research and calls for the rigorous evaluation of interventions which address multiple components (policy-level, system-level, therapy-related, patient-level, and adverse effect management). The 3 key questions are explicitly stated and very clear.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
PR #4	General	This report is very well structured and organized. The main points are clearly presented and reinforced. The conclusions inform a future research agenda and call for high-quality studies.	Thank you. No response necessary.
TEP #6	General	The report identifies that there is a paucity of high quality evidence based studies on adherence to Hepatitis C Treatment Interventions. It takes a highly rigorous approach to analyzing the existing literature to reach this conclusion.	Thank you. No response necessary.