Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Closing the Quality Gap Series: Comparative Effectiveness of Medication Adherence Interventions*

Draft review available for public comment from March 11, 2011 to April 8, 2011.

Research Review Citation: Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock S, Wines RCM, Coker-Schwimmer EJL, Grodensky CA, Rosen DL, Yuen A, Sista P, Lohr KN. Medication Adherence Interventions: Comparative Effectiveness. Closing the Quality Gap: Revisting the State of the Science. Evidence Report/Technology Assessment. No. 208 Part 4. (Prepared by RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-E010-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2012. Available at: 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=1248
Published Online: September 11, 2012

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Executive Summary	The structured abstract should be reorganized. It uses terms that are not defined until the body of the report, exemplified by the sentence, "All other outcomes were rated as low for benefit, low for no benefit, or insufficient." As noted above, this is easy to misinterpret as a statement about the effectiveness of the intervention rather than the quality of the evidence. The sentence "The number of interventions that provide low or moderate strength of evidence progressively decreases for health, health care utilization outcomes, and other distal outcomes" is also unclear– does this mean that there are fewer and fewer interventions of each type, of that they are less likely to produce low or moderate SOE? The results section of the abstract begins with the clinical interventions, then addresses the policy interventions, then returns to the clinical interventions. The conclusion addresses the important issue of sustainability of adherence interventions, but this issue is not alluded to previously in the abstract (and in fact gets little emphasis in the report as a whole).	Substantially revised the abstract so most of the comments addressing the strength of evidence statements are no longer relevant. The issue of long-term outcomes and applicability now receives expanded attention in the report.
Peer Reviewer #4	Executive Summary	Other than its length, several other issues with the Executive Summary deserve attention. Many of the tables could be eliminated since they are in the body of the report, or simplified to emphasize the main points. The authors note on p. ES-16 that multi-faceted interventions are compared with usual care, rather than directly comparing intervention components (e.g. through factorial designs, as they describe later). This reflects a long-standing debate between those who want to understand each component in isolation and others who emphasize that multiple interventions are typically required for behavior change. This debate should be acknowledged. On p. ES-18 they conclude that adherence interventions do not increase adverse events, but their summary of the evidence earlier on the same page indicates that there is insufficient evidence to draw conclusions. These statements seem inconsistent.	The executive summary is intended to serve as a standalone document, As a result some repetition between that document and the main document is to be expected and desired. We added some text to reflect this debate. Revised somewhat for clarity that the conclusion requires further confirmation

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Executive Summary	The structured abstract should be reorganized. It uses terms that are not defined until the body of the report, exemplified by the sentence, "All other outcomes were rated as low for benefit, low for no benefit, or insufficient." As noted above, this is easy to misinterpret as a statement about the effectiveness of the intervention rather than the quality of the evidence. The sentence "The number of interventions that provide low or moderate strength of evidence progressively decreases for health, health care utilization outcomes, and other distal outcomes" is also unclear– does this mean that there are fewer and fewer interventions of each type, of that they are less likely to produce low or moderate SOE? The results section of the abstract begins with the clinical interventions, then addresses the policy interventions, then returns to the clinical interventions. The conclusion addresses the important issue of sustainability of adherence interventions, but this issue is not alluded to previously in the abstract (and in fact gets little emphasis in the report as a whole).	Substantially revised the abstract so most of the comments addressing the strength of evidence statements are no longer relevant. The issue of long-term outcomes and applicability now receives expanded attention in the report.
Peer Reviewer #5	Executive Summary	The executive summary could use a little refining so that the key messages were clearer. The authors have clearly done a great deal of excellent work but I don't think it all comes across in the current format.	Revised for clarity
Peer Reviewer #8	Executive Summary	It would be preferable to define the limitations of scope immediately in the objectives. Presently, medication adherence, health, adverse events, and health care utilization are listed as the targets of the review for "chronic health conditions". However, because a number of exclusion criteria are used in the review and also because of the current state of the literature, the review provides guidance on only a set of specific health conditions- depression without psychotic features, hypertension, asthma, so on. The wording used here and through makes it sound as though the review should and does cover all health conditions but this seems inconsistent with the results that are presented. Shaping the review early as focused on a subset of possible chronic medical conditions would be helpful.	Revised to indicate that we are looking at an array of chronic conditions
Peer Reviewer #8	Executive Summary	Related to above, depression as a chronic medical condition is an interesting inclusion and has may unique features that may separate it from the other included conditions which are entirely medical. The authors should make a solid justification for why this is included as a chronic medical condition, specifically in terms of why other mental health disorders are not included here (e.g., non-psychotic disorders like anxiety, panic disorders, so on).	This justification is provided in the report; the abstract is limited in length
Peer Reviewer #8	Executive Summary	Provide the total number of manuscripts considered for review prior to reporting the total number included in the detailed review.	Revised as suggested

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Executive Summary	Define what is meant by "low evidence" prior to using this to characterize findings in results. It is unclear to readers if this means that the evidence base was insufficient in size or if it was well researched but had mixed findings or findings were consistent and poor.	Removed language relating to strength of evidence
Peer Reviewer #8	Executive Summary	The authors note that "We found evidence of effective interventions to improve medication adherence for all chronic conditions" which overstates the scope of the study. Revise to be more reflective of the conditions actually included in the review.	Results now list the chronic conditions for which we found evidence
Peer Reviewer #8	Executive Summary	The sentence noted above seems at odds with the sentence presented immediately before it- "….moderate or low evidence of benefit for medication adherence for 59% of these interventions." Can this be clarified?	Removed language relating to strength of evidence
Peer Reviewer #8	Executive Summary	The organization of the results is hard to follow. It seems to first target medication adherence results generally, then health outcomes, then perceptions of quality health care, the by type of intervention (policy level) related to adherence to medications, then perhaps back to medication adherence more generally in terms of patient target groups. Reorganization of the results so that readers can better follow the main findings would be helpful.	Revised to focus on bottom lines
Peer Reviewer #8	Executive Summary	The conclusions introduce the qualification "in the short term" but this is not mentioned in the results.	Removed language relating to strength of evidence
Peer Reviewer #8	Executive Summary	The "nested" nature of the results by way of condition and target group seems poorly represented in the abstract and otherwise well organized in the body of the review. The abstract would read better if the same general structure was adopted- where first intervention by condition are considered, then by intervention type, and then secondary questions about target groups.	We have revised the abstract substantially to show conclusions by clinical conditions as well as intervention
Peer Reviewer #8	Executive Summary	Background- the authors note that medication non-adherence is very common, but then go on to provide information that 20-30% of scripts are never filled and 50% of medications for chronic diseases are not taken as recommended. While this is a sizable proportion, it does not seem "very" common, which would suggest more than half of the population.	Changed to "relatively" common
Peer Reviewer #8	Executive Summary	Score and Key Questions: The scope seems over stated given the exclusion of key conditions like HIV and the eventual targeting of certain medication conditions for which data is available to form a strong evidence base.	Revised to say "across a broad array of chronic conditions"
Peer Reviewer #8	Executive Summary	Inclusion/Exclusion table: Do the authors mean "tertiary prevention for chronic diseases"?	We had intended to say "tertiary prevention of chronic disease" and elect to retain that language

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Executive Summary	A limitation in the results is the use of qualitative review and not meta-analytic approaches for conditions or intervention types that permitted this kind of review. While it is clear that culling across all identified studies would likely not provide valuable conclusions, it is likely that within certain areas it would be possible to estimate overall and specific effects. That being noted, the authors do a very good job at explaining their rationale and paths to conclusions for each section in the body of the document- thus as a qualitative approach it is well done. It would just be ideal if some sense of overall effects per condition could be estimated.	We have revised the table in the executive summary to give some sense of the magnitude of effect
Peer Reviewer #8	Executive Summary	Results of literature search: Provide key terms used in these searches.	We inserted a reference to the main report appendix.
Peer Reviewer #8	Executive Summary	Figure ES-2: Can K per medical condition be added here?	Unclear what reviewer meant?
Peer Reviewer #8	Executive Summary	Page ES-8 line 21- should “effective” be “promising” here?	We had intended the use of the word “effective” because the interventions showed a significant improvement in the intervention arm compared to the usual care arm.
Peer Reviewer #8	Executive Summary	Page ES-8 line 27- should Table ES-4 be Table ES-5 here?	We have revised tables and callouts.
Peer Reviewer #8	Executive Summary	Findings specific to clinical conditions: It would orient readers here if the specific conditions were listed.	The table is now revised and lists clinical conditions in order.
Peer Reviewer #8	Executive Summary	Findings specific to interventions: The authors note that the most consistent evidence on adherence was for certain conditions. This seems a more appropriate conclusion for the section looking at interventions within conditions. The findings on intervention types should focus on intervention approaches that appeared more effective across medical conditions. More the second part of this section of text.	We have revised this section as suggested
Peer Reviewer #8	Executive Summary	Page ES-10 line 10- The text notes a single example not multiple. Change to “This example illustrates.”	Revised the text
Peer Reviewer #8	Executive Summary	Page ES-15 line 52- Typo? Space missing in “1 to 30”	Revised
Peer Reviewer #8	Executive Summary	Page ES-16 line 22- Typo? Decision making is in text in this paragraph as both ‘decision-making’ and ‘decisionmaking’	The word is hyphenated when it is an adjective, as per AHRQ standards
Peer Reviewer #8	Executive Summary	KQ 4: The authors conclude that they did not find any evidence for certain vulnerable populations. Does this mean that there was no evidence base or that there was a sparse evidence base that suggested no benefit?	Revised for clarity
Peer Reviewer #8	Executive Summary	KQ 5: line 24- Consider adding “negative”- ….unintended negative consequences.	Added as suggested
Peer Reviewer #8	Executive Summary	Type page ES-19 line 22- delete second minimalist?	Revised the text

Source: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1248
Published Online: September 11, 2012

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #8	Executive Summary	Results of literature search: Provide key terms used in these searches.	We inserted a reference to the main report appendix.
Peer Reviewer #9	ES-18, line 13	"low strength of evidence of no benefit of interventions on adherence" - does this mean there is benefit or does this need to be edited?	Revised to state insufficient evidence
Peer Reviewer #9	ES-19, line 22	"spanned the range from minimalist to intense and minimalist" - what does this mean	Revised
Richard Chapell	Executive Summary	Our comments on the applicability of the conclusions of the review, discussed below, should be reflected in the corresponding section of the Executive Summary as well as the structured abstract. Page ES-15 typo: "to30"	All changes in the full report are reflected in the executive summary
Dee Simons	Executive Summary	N/A	NA
Peer Reviewer #1	Introduction	The purpose is clear	Thank you
Peer Reviewer #2	Introduction	The introduction and background info are fine.	Thank you
Peer Reviewer #3	Introduction	Page 1 - 3 of intro (41 - 43/676 overall) has the problem of repeated sentences beginning with "moreover" and "also." On page 3 the italics first introduced in line 18 are used inconsistently, so as a reader it is not clear to me what distinctions are being made. At the transition of sections on the bottom of page 4 of the Introduction the flow becomes more clear. The bulleted list of strategies makes it easier for the reader to see the overall flow of the argument.	We have revised this section to eliminate the repeated use of “moreover” and “also.” We have also made revisions in the section where we first introduce the use of the four terms in italics by numbering/listing them. We have also bolded them throughout this section to draw attention to their continuity.
Peer Reviewer #4	Introduction	The background section of the report itself is disorganized. It might benefit from the common approach in grant applications of providing subheadings to indicate the topic of that section.	We have added subheadings to this section to indicate the topic of each section to assist with organization.
Peer Reviewer #5	Introduction	Well-written Not sure that the estimated $100B cost of non-adherence is based onstrong evidence- given the rigor of the review, this assertion needs to be better justified and examined	Thank you. We added some additional citations to support this figure.
Peer Reviewer #5	Introduction	Page 5: would be good here to have a table of all of the 16 components from DeBruin	We have added this table as suggested.
Peer Reviewer #5	Introduction	Page 10 - would have been good to include this list intervention types in the executive summary	We elect to leave this table in the main results because we believe that a lengthy list of DeBruin’s components may lead readers to assume that our intervention clusters build directly on these components
Peer Reviewer #7	Introduction	The introduction was clearly written and easy to follow. In general though, much of the same information was repeated in the discussion.	We have reviewed the discussion for overlap with the introduction and do not find any.
Peer Reviewer #9	Introduction	Provides a useful overview of the nature of the issue and the purpose of the report	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #10	Introduction	Well written and clear synopis of the problem, charge and approach. It is very clear how this reviews differs from previous work and the contribution it is designed to make to the literature and practice.	Thank you
Richard Chapell	Introduction	N/A	NA
Dee Simons	Introduction	N/A	NA
Peer Reviewer #1	Methods	I find the inclusion and exclusions to be valid and the criteria appropriate. I do not believe specific statistical methods were used??	Thank you; that is correct
Peer Reviewer #2	Methods	I am concerned that the review included ONLY RCTs to answer the clinically-relevant questions. There have been some well-conducted observational studies of medication adherence. I believe that you missed relevant and valid information by uniformly excluding studies that were not RCTs. I suggest that you broaden the inclusion criteria to include observational studies that used a quasi-experimental design (i.e., had a control group) and that used appropriate statistical techniques for reducing selection bias.	Based on guidance provided by the AHRQ Methods Manual, we judged the value of observational studies to this evidence base by first considering the volume of RCT evidence and then evaluating the value added by observational studies. We judged that this area of research had a high number of RCTs for patient, provider, and systems interventions, but not for policy interventions. In accordance with this methodological guidance, we did include all study designs for questions of effectiveness of policy interventions. For questions relating to the effectiveness of other types of interventions directed at the patient, provider, or the system, we wanted to ensure that included studies could clearly attribute changes in adherence to the intervention and therefore limited the evidence of RCTs. In addition, we found a tension in this review between extensiveness and usability of results, in that the broader range of study designs included, the greater the heterogeneity of outcome measures, intervention models and study populations. Including non-RCT designs would have tipped the balance even more toward an overwhelming degree of heterogeneity soas to reduce usefulness of review results.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	The methods are appropriate and are well laid out. This is a very broad topic, and the search strategy is challenging. The inclusion and exclusion criteria are reasonable. There may be pushback about not including HIV, since many adherence studies have been done in that area, but I think the justification provided in this section is reasonable. While more quantitative syntheses would be nice, the authors' argument about heterogeneity (page 17) is compelling and I think they made the right decision.	Thank you
Peer Reviewer #4	Methods	Summarized in general comments	Thank you
Peer Reviewer #5	Methods	Exclusion of primary prevention studies doesn't make sense to me (it relies on semantic decisions about what constitutes a disease - e.g. hyperlipidemia)	We elected not to include studies of primary prevention because the incentives to adhere are different than among patients who have already been identified as having an existing condition. While we agree there are some diagnoses, such as hyperlipidemia and osteoporosis, that also constitute risk factors for other conditions and for which it may be less clear that treating them is secondary prevention/treatment, we have elected to include these conditions because they do constitute an unhealthy existing diagnosis.
Peer Reviewer #5	Methods	Exclusion of studies from Western Europe is potentially problematic as well	We excluded studies from Western Europe because the health care system in those countries had major differences with US systems with regard to factors (such as payment for medications) that can markedly affect medication adherence.
Peer Reviewer #5	Methods	The rationale for not performing quantitative synthesis within sub-groups of studies is not strong- for example, why not synthesize the effect of pharmacist interventions on blood pressure?	We had prespecified that we would not perform quantitative synthesis for subgroups that have results from fewer than 3 studies; in this subsection to which the reviewer refers, we only have results from 2 studies.
Peer Reviewer #7	Methods	The inclusion/exclusion criteria were justifiable and the search strategies were explicitly stated and logical. the appendices were quite helpful in determining the search strategy used and understanding which studies were excluded. The definitions for outcome measures were appropriate and given the heterogeneity of studies, the review was primarily descriptive.	Thank you
Peer Reviewer #7	Methods	May want to consider that pharma trails involving adherence as secondary outcomes were not included	We added text to our limitation section to address this issue.
Peer Reviewer #9	Methods	The inclusion and exclusion are appropriate.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Methods	The search strategies appear to be comprehensive within the scope of the report.	Thank you
Peer Reviewer #9	Methods	There could be more detail provided on the risk of bias assessment. For example pg 16 line 52-53 "proper research design". A clinical reader may not know what this means; pg 16 line 55 ITT analysis again a clinical reader may not know that refers to intention to treat, may not know what that means, or understand why that is important; line 52 pg 16 "information bias" is not a commonly used term in research methods - could alternative terms be used to further explain this form of bias, eg internal validity etc. Also there might be a more detailed explanation of criteria for grading strength of evidence. There is more than one method of doing this, so a more detailed discussion of a representative study design that would fit in each of the four categories would be useful.	We added information in the methods chapter on definitions of ITT analysis, information bias, and detection bias.
Peer Reviewer #10	Methods	The exclusion criteria may be too broad. The two areas that I think were a problem are the exclusion of HIV/AIDS and non-randomized studies. HIV/AIDS is now a chronic disease. People with HIV/AIDS are living to have the same chronic diseases as everyone else. It is also is the area in which the most adherence research has taken place. the exclusion of HIV/AIDS is problematic as it ignores a large literature that should be applicable to other chronic diseases.	See response above regarding exclusion of HIV studies
Peer Reviewer #10	Methods	The other exclusion that may be problematic is non-randomized trials. Although this is not the best scientific approach, many adherence studies are done in clinical settings or have a policy approach where a non-randomized design is common. The importance of the exclusion is not clear from the exclusion table because 2913 reports were eliminated but the breakdown is not included. Including the exclusion numbers with reasons (as was done for the full-text articles) would help the reader better decide the generalizability of the study and could determine the need to explore non-randomized work.	See response above regarding exclusion of nonrandomized studies
Richard Chapell	Methods	Page 14 Study inclusion/exclusion criteria appear to be unnecessarily stringent. Over 40,000 articles have been published on adherence, including 41 systematic reviews and 22 meta-analyses of which we are aware. The present review only encompasses a fraction of this literature. Most importantly, limiting searches to publications from 1994 to present has no apparent purpose other than to reduce the amount of material to be reviewed to a manageable size. If there are methodological reasons for this and other exclusions, please state them. If the size of the literature is being restricted for reasons of time and budget, this fact must be acknowledged, and the limitations this imposed on the applicability of the review must be discussed. Please include text describing the purpose behind the study inclusion and exclusion criteria.	We included a lengthy section in chapter 1 entitled “scope of the review” which explains our decisions.

Commentator & Affiliation	Section	Comment	Response
Dee Simons	Methods	N/A	NA
Peer Reviewer #1	Results	The authors are to be commended for an extremely complete review. The characteristics of the studies are clear.	
Peer Reviewer #1	Results	My main issue is that I find a lot of redundant statements on findings and results repeated several times within the report. I believe some of these could be eliminated and the length reduced.	We reduced redundancy by discussing studies in the clinical area for the medication was prescribed. We reduced repetition in KQ 4 and 5 as well by referring to KQ 1 results when possible and by organizing them differently.
Peer Reviewer #1	Results	Other specific comments follow: 1. I may not have identified all of these issues but I was distracted by things like depression care covered under diabetes and lipids (page 81)?	See above, we have eliminated such redundancies
Peer Reviewer #1	Results	2. Page 83, line 41: why are oral hypoglycemics mentioned here?	See above
Peer Reviewer #1	Results	3. Blood pressure intervention pages 99-100. I do NOT expect most interventions to influence diastolic blood pressure. This is because in most studies, many of the patients have normal or controlled diastolic BP at baseline (these patients have isolated systolic hypertension). In most of these cases, medication reduces systolic BP much more than diastolic, by definition. I think some mention of this fact is necessary since I would not expect a "normal" diastolic BP to be much improved.	Thank you for this comment, we agree, diastolic blood pressure is less likely to be influenced by most interventions. We have acknowledged this within the Hypertension section.
Peer Reviewer #1	Results	4. Again, page 101, lines 33-36: why is depression and oral hypoglycemics mentioned under hypertension?	See above
Peer Reviewer #1	Results	5. page 161, line 4: why is HA1c mentioned as a biomarker for depression and later BP? This does not make sense to me. There likely are other similar examples throughout the report.	See above
Peer Reviewer #2	Results	Considerable detail was provided on all of the analyses and I was able to find relevant info on all of the included studies. However, the report is so long and includes so many sub-sections, that is got confusing at times to understand how one sub-section differed from another. However, the executive summary did give a more succinct summary of the report.	We have tried to reduce the complexity of the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	The results are thoroughly presented and the studies are very well described. To me, the challenge of this section, and of the review overall, is finding the right level of detail. This results section is incredibly dense with information. It can serve as a useful reference for anyone planning an adherence study, especially if the study is focused on a given clinical area, since the person planning the study can identify and read the specific relevant section. For readers interested in a general overview of adherence, this is very difficult sledding. Really this is an over-arching decision about how to structure these types of reviews, if the thought is that most general readers will stick to the ES and that this results section will be used more a reference document for looking up specific areas, then it works well.	We have attempted to simplify the presentation in the results chapter by starting with an overall table that summarizes the effects through simple notation indicating benefit, harm, and no difference
Peer Reviewer #3	Results	So the results and appendices are more than adequate, my concern is really about whether they are too much. In terms of the studies included, the list seems reasonable to me. The challenging issue will be timeliness. Adherence is a hot topic now and there are many new papers coming out in 2011-2012, which will be a concern for the relevance of this report. For example, there are only 3 policy papers found here, but there was at least one new major paper last month (Choudhry in NEJM) and are likely to be many more.	We added the suggested paper to the policy interventions section
Peer Reviewer #4	Results	The extensive tables contain much useful information, but in aggregate are so detailed as to be almost unusable. For example, Table 6, p. 29 of the report is very difficult to read and interpret because of its formatting. Users will want to compare baseline and follow-up measures between intervention and comparison groups, but they need to read vertically rather than horizontally to do so.	Revised all summary tables for medication adherence outcomes to show baseline and followup values
Peer Reviewer #4	Results	Careful attention to terminology will help clarify the presentation. For example, on p. 23 the statement "We found eight articles reporting on seven randomized trials that assessed the effects of six different interventions aimed at improving medication adherence among adult patients with diabetes mellitus. Six studies had a medium risk of bias and one study had a low risk of bias" is confusing because they use both "trials" and "studies" rather than a single term.	Revised to ensure that KQ 1 consistently refers to trials
Peer Reviewer #4	Results	While their reluctance to conduct quantitative synthesis of the literature is understandable, it does create problems of interpretation. For example, on p. 59 they state that the evidence for effectiveness of adherence interventions in hypertension is "mixed" because 7 of 15 studies demonstrated effectiveness. This conclusion disregards study size, strength of design, and magnitude of effect – considerations that a traditional meta-analysis would take into account.	We used the term limited to refer to lack of evidence and inconsistent to refer to opposing conclusions in our revisions As noted above, the summary tables on strength of evidence now include study size and magnitude of effect that illustrate how we used multiple domains to arrive at a final SOE grade.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The report could be shorted by limiting the amount of detail when only a single study addresses a specific disease. Their commitment to using the same format for all diseases seems cumbersome when there is scanty evidence. Similarly, “synthesizing” a single study or studies of very different designs (e.g. the heart failure studies on pp. 85-7) seems unnecessary.	Thank you for pointing out this opportunity to reorganize our results sections. While we still believe that the single study for myocardial infarction and the four heart failure studies are different enough from other studies in the cardiovascular disease section to synthesize separately, we have reorganized these sections with the intention of making them less cumbersome for readers.
Peer Reviewer #4	Results	The authors could clarify the nature of adherence interventions for multiple chronic conditions (vs. a single condition) on p. 157 by more fully describing the rationale for such studies as defined by the investigators. In such studies, interventions are designed to improve adherence with complex regimens in their entirety – a useful goal.	We added some text to the results section to describe the nature of this cluster
Peer Reviewer #4	Results	While Key Question 4 is very important, many users will want to know whether a particular intervention is as useful in a vulnerable minority population as it is in a majority population. Thus, they will be interested in the subgroup analyses of the 3 interventions that included both populations (p. 190).	Our understanding is that the reviewer would like to compare vulnerable and overall populations. To avoid repetition (with material presented in KQ1), we have retained only subgroup analysis for KQ 4 for the three studies in which the vulnerable population is a subgroup of the overall study population (Please note that in KQ4 we present overall results for the twelve trials in which the entire study was conducted in vulnerable populations)
Peer Reviewer #5	Results	The results section is hard to read- I would prefer each section start with a succinct summary of the effects noted, then go into the details. Also, the evidence tables are hard to read and require constantly going between tables to interpret them. I found myself wishing that each section be written more like a journal article. The table structure leads to the need for several pages to describe each study- not very efficient (and creates an overall report of 600+ pages to describe 57 studies!)	We have attempted to simplify the presentation and table structure.
Peer Reviewer #7	Results	The amount of detail presented in the result section appropriate. The tables were a little hard to follow and discern which were the intervention groups and which were the control. The labels were all clear. did not see any relevant studies that were not considered.	Thank you, we have revised the table structure.
Peer Reviewer #7	Results	A couple of typos page 83 of 676	Thank you, these errors have been corrected in our revised report.
Peer Reviewer #7	Results	page 97 line 36	Thank you, this error has been corrected in our revised report.
Peer Reviewer #7	Results	table 71 Rudd study, no p-values reported	Revised

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Results	Overall the results are fine. There could be a summary of the results provided at the beginning or end of the section as there is much detail to integrate to take away a more overall message.	Revised as suggested, each Key Points section includes an overall summary of the direction of effect for each outcome for each study
Peer Reviewer #10	Results	The amount of detail is good. the tables of studies and outcomes would be better if results and studies were on the same page. You cannot link the results to the studies in the current format. Could they be done in a landscape format? Also, being more clear about the outcome measure in the results column would help. Can the measure and outcome columns be merged See my comment above about excluded studies	Revised as suggested
Richard Chapell	Results	Page 40 and throughout the review: The terms "limited" and "mixed" evidence are used without being defined. "Mixed" is especially problematic because it could mean that treatment effects appear on both sides of the zero line or that they are all on the same side of the zero line but some are not statistically significant. Please define these terms. Page 59: Grammar: "Involved" should be "involving"	See above, we revised the report to avoid the use of the term “mixed”
Dee Simons	Results	Table 67. Change Berger, et. al., 2009 to Berger et. al., 2005 Table 68. Change Berger et. al., 2009; footnote 144 to Berger et. al., 2005; footnote 136	Revised
Peer Reviewer #3	Discussion	The discussion was the strongest and clearest part of the review. For KQ1 especially, which covers a large range, the discussion broke it down into short sections and the summary tables were reasonably easy to follow. This section feels like something that a reader with general interest could go over and come away with a good sense of where the field is now and what remains to be done.	Thank you
Peer Reviewer #8	Discussion	Given the findings, it seems overly conclusive to note that a pharmacist should provide the adherence management for care of hypertension. Is it clear in the results that the deliverer of medication/adherence management needs to be a trained pharmacist?	We have revised the text to indicate clearly where the intervention hinges uoin the deliverer
Peer Reviewer #8	Discussion	Given that the number of conditions not reviewed exceeds what is mentioned here, it may be better to frame this in terms of what the scope of the review was limited to and that other conditions falling outside of that are not represented.	We have added text describing the limitations around conditions
Peer Reviewer #8	Discussion	Consider including the need for reporting of AEs in behavioral interventions in the research gaps area.	Yes, we have included this point
Peer Reviewer #8	Discussion	Can the authors recommend what would define a minimum length of follow-up for research to better characterize “long-term” health outcomes?	We added some text explaining our preference for long outcomes at 1 year or greater
Peer Reviewer #9	Discussion	The report is well structured. The discussion section, however, could highlight the main points that are relevant to practice and those relevant to future research.	We are separating sections on methodological limitations from research gaps.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Discussion	Missing in the methodological limitations is attention to the heterogeneity of measures and definitions - a significant limitation in the literature (pg 212 lines 15-37.)	Already discussed in the first paragraph under methodological limitations
Peer Reviewer #9	Discussion	Implications for clinical and policy decisionmaking or methodological limitations (pg 211-212) should mention the limited work examining the relationship of adherence and clinical outcomes.	We have discussed this issue under methodological limitations.
Peer Reviewer #9	Discussion	I think there needs to be a separate section in the discussion, clearly labeled, summarizing the many recommedations for future research to both strengthen studies (design) as well as to provide the replications that were noted to be missing and to address missing areas.	We summarized some cross-cutting themes in the future research section
Richard Chapell	Discussion	As discussed above under "Methods," the literature on adherence is considerably larger than the literature discussed in the present review. Please include a discussion of the size of the literature and the implications of assessing only a fraction of it in the discussion of the Limitations of the Comparative Effectiveness Review Process. These implications include the possibility of failing to identify an effective adherence program or of rating the available evidence supporting a given conclusion as weaker than it may actually be. Page 206: "Minimalist to intense and minimalist" This is probably a cut/paste error.	See above regarding explanations about the scope of the review. We have added text to our discussion section explaining our limitations.
Dee Simons	Discussion	N/A	NA
Peer Reviewer #8	Conclusions	Add management to “pharmacist-led hypertension management approaches”. Also, as noted previously, none of the other intervention approaches noted identify a deliverer- it is not clear if the authors suspect that the deliverer in this case is a critical component.	In general, we have revised to reduce focus on the agent of delivery, but in this instance, yes, the agent is a unique characteristic of the intervention
Richard Chapell	Conclusions	N/A	NA
Dee Simons	Conclusions	N/A	NA
Peer Reviewer #1	Discussion/ Conclusion	I believe these are clearly stated. Again, some of these are stated several times throughout the Executive Summary, text and discussion and some of these might be condensed. I understand why they excluded the paper by Carter BL, Pharmacotherapy 2010;30:228-235. However, why was the primary study that did include pill counts and adverse effects not considered? That paper is: Carter BL, et al. A cluster-randomized trial to evaluate physician\pharmacist collaboration to improve blood pressure control. Journal of Clinical Hypertension 2008;10:260-271. The future research section is very important and I believe that it is complete.	Thank you for this comment. We reviewed the trial Carter BL, et al. A cluster-randomized trial to evaluate physician/pharmacist collaboration to improve blood pressure control. Journal of Clinical Hypertension 2008;10:260-271. This trial was not included in our final report because reviewers deemed it at high risk of bias. The criteria that led to a determination of high risk of bias included: no information on allocation concealment, physician referral of patients to the trial, no blinding of patients and physicians, and important baseline differences in medication adherence between the intervention and control groups.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion/ Conclusion	I am concerned that your conclusions are based only on RCTs for the non-policy questions and because each sub-section or sub-question only included a few RCTs. The RCT findings may not be reflective of the broader set of studies on adherence interventions. Your broad conclusions about effectiveness of nurse-driven or pharmacist-driven interventions are based on a few disparate RCTs, and may not reflect the level of nuance that is necessary to optimally design a multi-faceted plan for supporting medication adherence for chronically-ill patients. By including some studies that used quasi-experimental design, it may allow a better understanding of how differing types of nurse-driven or pharmacist-driven interventions have differing effects on adherence.	See response to the earlier comment about the decision to limit this review to RCTs for most intervention types. We acknowledge that that the decision to limit the review to RCTs for patient, policy, or systems interventions represents a limitation of the review. We do, however, believe that the potentially greater applicability of observational studies needs to be balanced by the higher likelihood of risk of bias. We intend to raise the issue of this balance when discussing future research needs, particularly for practice-driven changes to systems such as nurse- and pharmacist-driven interventions. For such interventions, a review of hypotheses-generating research may be useful in identifying specific areas for more rigorous research and we have included the suggestion for such research in our future research needs.
Peer Reviewer #3	Discussion/ Conclusion	In terms of the future research orientation, the authors highlight some of the important considerations, if appropriate this may be a place to say more about the additional research that is being published and will be published during 2011-12 and which readers will need to consider in addition to the material covered in this report.	We ran an update search at the end of 2011 and have included additional studies. As with other active areas of research, ongoing trials have the potential to shift the weight of evidence: this systematic review will need to be updated frequently.
Peer Reviewer #4	Discussion/ Conclusion	Summarized in general comments	Thank you
Peer Reviewer #5	Discussion/ Conclusion	The discussion and conclusion are reasonably clear	Thank you
Peer Reviewer #5	Discussion/ Conclusion	Given the scope of the review, it is hard to know if any relevant literature has been missed	Thank you
Peer Reviewer #5	Discussion/ Conclusion	Future research section is good	Thank you
Peer Reviewer #7	Discussion/ Conclusion	The implications of the major findings are clearly stated; however, the general conclusion is further research is needed in specific areas, but there are limited recommendations made.	We have expanded our section on recommendations.
Peer Reviewer #7	Discussion/ Conclusion	The limitations of the review/studies are described adequately.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Discussion / Conclusion	I wonder if effect sizes should be reported for the studies included in the review so the reader can gain some perspective on the magnitude of effect of the studies which did show improvements.	A preliminary assessment suggests that a significant proportion of the studies in our review do not provide sufficient evidence to calculate effect sizes; we would need to contact authors for additional detail and that step is outside the time and resource constraints of this review.
Peer Reviewer #10	Discussion/ Conclusion	The main findings are clearly stated. It would help to have a brief abstract at the start of the executive summary. See the above comments about the tables to make the report more readable.	The report does include an abstract. We have revised tables for the executive summary.
Richard Chapell	Figures	N/A	NA
Dee Simons	Figures	N/A	NA
Richard Chapell	References	N/A	NA
Dee Simons	References	N/A	NA
Richard Chapell	Appendix	N/A	NA
Dee Simons	Appendix	N/A	NA
Peer Reviewer #1	General	I think I covered structure and organization above. The main points are clear and the conclusions should inform both polity and practice.	Thank you
Peer Reviewer #1	General	This report is very meaningful and appropriate. The population is very well defined and the key questions are appropriate	Thank you
Peer Reviewer #2	General	The report was extensive and covered many key points; however, its usability is limited because the few RCTs had substantial homogeneity in the study populations, measurement of adherence and intervention models.	We agree that the heterogeneity in this field is a limitation.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	The key questions addressed in the project were appropriate. In general, the report focused on the most relevant areas for medication adherence. One notable exception was adherence to HIV/AIDS medications. Although HIV/AIDS is an infectious disease, it is managed as a chronic illness. Additionally, there are numerous studies that have shown the importance of medication adherence to clinical outcomes for HIV/AIDS patients so there would be sufficient studies to include in this project. Furthermore, CMS has now included adherence measures for HIV antiretrovirals in its safety reports to Medicare health/drug plans. I think that this AHRQ report has a major gap by not including HIV adherence studies.	We completely agree that HIV/AIDS is managed as a chronic disease and that antiretroviral adherence is a critical aspect of health outcomes in its treatment. Our decision not to include it in this review was not so much that it is an infectious disease as that there have been several recent outstanding systematic reviews with very recent updates (cited below in this cell). To avoid duplication, we elected not to include HIV/AIDS. We do agree that the previous knowledge acquired in adherence intervention studies for HIV/AIDS can inform adherence interventions for other chronic illnesses. Hence we have added to the discussion information regarding the existing reviews of HIV/AIDS adherence intervention RCTs and how they related to our findings. **Recent HIV reviews** Antiretroviral adherence interventions: translating research findings to the real world clinic. http://www.ncbi.nlm.nih.gov/pubmed/20425057 Simoni JM, Amico KR, Smith L, Nelson K. Curr HIV/AIDS Rep. 2010 Feb;7(1):44-51 Efficacy of interventions in improving highly active antiretroviral therapy **adherence** and **HIV**-1 RNA viral load. A meta-analytic review of randomized controlled trials. http://www.ncbi.nlm.nih.gov/pubmed/17133201 Simoni JM, Pearson CR, Pantalone DW, Marks G, Crepaz N. J Acquir Immune Defic Syndr. 2006 Dec 1;43 Suppl 1:S23-35 Antiretroviral adherence interventions: a **review** of current literature and ongoing studies. http://www.ncbi.nlm.nih.gov/pubmed/14724327 Simoni JM, Frick PA, Pantalone DW, Turner BJ. Top HIV Med. 2003 Nov-Dec;11(6):185-98. **Review**

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	In terms of clarity and usability, I found the discussion/conclusion to be very strong and felt that the structured abstract and ES were not as clear. Perhaps the range of topics covered by the KQs and the heterogeneity of the literature make it difficult to collapse everything into a short abstract.	The executive draws from the revised discussion. We have revised the abstract to ensure better signposting, as noted above.
Peer Reviewer #3	General	In the ES, often the writing in the background sections for each KQ was a bit loose and repetitive and could be tightened up, the conclusion paragraph (page ES-20) was an effective summary and call to action.	We have substantially revised and edited the text
Peer Reviewer #3	General	As noted, the overall (p201-216) was the strongest part, so would use that as a guide for punching up the ES and abstract.	We have revised the discussion, abstract, and executive summary.
Peer Reviewer #3	General	The review provides a useful overview of the adherence literature. Making clear statements of the target populations is challenging since adherence is a general behavior that cuts across multiple clinical conditions. In this circumstance, KQ's 1, 2, and 3 each have important differences and cannot easily be forced under one framework. Attempts to put these KQs into a single framework make the review, in places, harder to follow. I would suggest signposting clearly that there are distinctions between the KQs and then dividing the results more explicitly. I am referring here to the abstracts and summaries, which is where most readers will be focusing; in the extended text each of these sections is of course separated, but those are so long that few readers will go through it all. KQ's 4 and 5 don't add much but presumably needed to be covered since they were prespecified.	Our methods section explains the differences in approach for KQ in the executive summary. We have clearly indicate the KQs in the abstract.
Peer Reviewer #3	General	As this document is edited, some attention should be given to the writing style and attempting to remove occasionally repetitive phrasing. In various places there are frequent sentences starting with "moreover" and in other sections "also." This is hard to avoid in systematic reviews, but some attention to this will greatly enhance the readability for general audiences. The style issue is more of a concern in the earlier parts of the document, the discussion/conclusion is strong.	We have edited the document to cut down on these instances.
Peer Reviewer #4	General	In revising this report, the primary emphasis should be on improving its clarity and usability, as described above. The authors have conducted a painstaking review of the literature, and the information in the report is of great relevance. In my comments, I have quoted specific sentences only to provide examples of the need for a thorough rewrite.	We have revised and heavily edited the report for readability.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	General Comments: The authors of this report have undertaken the daunting task of synthesizing a heterogeneous set of studies about interventions to improve medication adherence. Strengths of this review include: 1. The importance of the 5 key questions, and particularly the novelty of key questions about variations in intervention design, impact on vulnerable populations, and adverse effects (Key Questions 3-5), which are not typically addressed in synthesis of the adherence literature	Thank you
Peer Reviewer #4	General	2. The well-described search strategy and comprehensive assessment of adherence interventions conducted in the US	Thank you
Peer Reviewer #4	General	3. The organization of papers by disease state in the responses to Key Question 1 will be valuable to individuals considering adherence interventions	Thank you
Peer Reviewer #4	General	4. The timeliness of the review, given the incorporation of adherence measures into Medicare Advantage quality ratings	Thank you
Peer Reviewer #4	General	5. The useful approach to organize the components of interventions (well summarized in Figure 3 on p. 173	Thank you
Peer Reviewer #4	General	6. The demonstration through Key Question 5 that little attention has been paid to potential adverse effects of adherence interventions – an important area for further study.	Thank you
Peer Reviewer #4	General	There are offsetting weaknesses with the draft report, however. 1. The first is simply its length – a report of over 600 pages describing only 60 studies. Because the review is so detailed, general conclusions about the comparative effectiveness of interventions are routinely lost in the mass of details about individual studies. This will limit its usefulness. As an example, even the Executive Summary is 20 pages long – requiring far more time than someone wishing to gain a quick overview of the issues will be willing to invest.	All the required elements of this review make it difficult to substantially reduce the size of the appendices, which account for most of the page in this document. We have attempted to shorten and simplify the tables in the results chapter.
Peer Reviewer #4	General	2. Problems with the quality of the writing compound the problem of length. A strong editorial hand could simplify and clarify important take-home messages such as one on p. ES-8: “Despite evidence suggesting that several interventions offer promising approaches to improving medication adherence, evidence exists for only a subset of these effective interventions showing that the improved adherence is accompanied by improvements in other outcomes, such as biomarkers, mortality, morbidity, quality of life, patient satisfaction, health care utilization, costs, or quality of care.” Something as simple as “Only a subset of interventions that improve adherence also demonstrate improvements in other outcomes”.	Revised

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General	3. Because the report does not provide any quantitative synthesis of findings from studies that address the same clinical condition, the report cannot address the important question of how much improvement in adherence is necessary to produce a clinically meaningful improvement in outcomes (for example, reduction in systolic BP). Potential users can glean this information from the tables that summarize the studies, but it requires substantial effort.	The specific issue raised by the reviewer, of how much adherence is necessary to produce a clinically meaningful improvement in outcomes is very important, but is outside the scope of this review.
Peer Reviewer #4	General	4. At times, the authors blur the critical distinction between strength of evidence, which is a function of study design, and strength of effect, which is a measure of the outcome differences between treatment arms. For example, it is not clear whether the sentence in the structured abstract, "we found moderate or low evidence of benefit for medication adherence for 59 percent of these interventions" refers to the fact that 59% of the studies had moderate or low strength of evidence, or that 59% of the studies found improvements in adherence.	We have revised the strength of evidence tables in the executive summary to include magnitude of effect. We hope that our revisions will clarify that our SOE ratings were based on a combination of factors, including study design and strength of effect.
Peer Reviewer #4	General	5. The decision to stratify the report by clinical condition is a mixed blessing. As noted above, individuals designing interventions for particular conditions will find this helpful. On the other hand, individuals who want to design interventions for other disease or combine single strategies into multi-faceted interventions will have difficulty using the report to compare possible approaches. A second consequence of the decision to organize the report by disease is that the "cell size" becomes very small, as shown in Table ES-5. This results in substantial repetition in the body of the report. The decision makes little sense in Key Question 3 (e.g. p. 162 of the report), since policy interventions are typically not disease-specific.	We revised KQ 2 (which we understand the reviewer to refer to as the policy intervention KQ) to refer to overall intervention rather than clinical condition,
Peer Reviewer #4	General	6. While the decision to exclude studies of adherence in HIV makes their task more manageable, it also eliminates much of the most innovative adherence research in the US in the last 10-15 years. The findings of these studies have important implications for adherence interventions for other chronic health conditions. The rational on p. 210 that HIV is an infectious disease is not compelling, since advances in treatment have converted HIV into a chronic health condition with many similarities to the conditions included in this report. Comparison of the conclusions of this review to recent syntheses of HIV interventions would be instructive.	See previous response on the exclusion of HIV studies

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	This report reflects a great deal of work on the very important topic of medication adherence interventions. The authors have used well-defined and rigorous methods to conduct their review. They identified 57 relevant studies, mostly randomized trials, across several chronic conditions. Overall, interventions, of several types, improved adherence, but in many cases the strength of evidence was rated low or medium. The report would benefit from a greater degree of synthesis across conditions, with more focus on the types of interventions most likely to be successful. In addition, the method of organizing the evidence tables is not helpful in the absence of meta-analysis- I found myself wishing for a single table for each clinical area that included all key features and results.	We revised all KQ 1 sections to provide a summary overview of the direction of effect of studies in the key points section.
Peer Reviewer #7	General	Yes, the report is well structured and organized. The main points are clearly presented. The conclusions are not likely to directly impact or inform policy or practice decisions.	Thank you
Peer Reviewer #7	General	The target population and audience were explicitly defined.	Thank you
Peer Reviewer #7	General	The key questions are appropriate and explicitly stated	Thank you
Peer Reviewer #7	General	The report is well written and addresses an important topic. Unfortunately, because of the heterogeneity of the studies focusing on adherence, there are minimal clinically meaningful recommendations that can be made.	We have reviewed interventions across clinical conditions to make more policy relevant conclusions
Peer Reviewer #8	General	This formidable synthesis seeks to quantify and characterize medication adherence promotion interventions found effective in the literature. The scope is extensive and results help to guide both practice and research. While the executive summary, and the portions reviewed of the body of the review, are well written and concise, the abstract is difficult to follow and could be improved in organization and clarity. Specific comments and suggested relative to the ABSTRACT and EXECUTIVE SUMMARY are provided below. Overall, the amount of work leveraged to create this document is evident and the conclusions in the body of the work and execute summary are generally well explained.	Thank you
Peer Reviewer #9	General	The key questions are appropriate	Thank you
Peer Reviewer #9	General	My reading of the results would suggest that there is too little definitive evidence to influence policy and there is limited evidence to influence practice.	Our revisions draw out additional policy relevant findings
Peer Reviewer #9	General	The report is clinically meaningful. The target population is clearly defined. It would be useful to put the target population in the title e.g. comparative effectiveness of medication adherence in chronic disease	Thank you
Peer Reviewer #10	General	The report is clinically meaningful. The targets are all well-defined and the key questions are appropriate.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #10	General	The report is well-structured and clearly stated. It can be used to inform policy.	Thank you
Richard Chapell	General	N/A	NA