Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Assessment and Management of Chronic Cough*

Draft review available for public comment from June 12, 2012, to July 10, 2012.

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Comments to Research Review

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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.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	The key questions are appropriate and explicitly stated. The audience of this report is not explicitly stated but assumed based on the general description of the Effective Health Care Program at the beginning of the executive summary (p ix) that the audience is consumers, health care providers, and policy makers.	Thank you
Peer Reviewer #2	General	The report reflects extensive work and organizational efforts. Also, not unanticipated but important to delineate as has been done regarding KQ1 and KQ2 is the “limited” evidence to the questions at hand. But, I have several concerns: Both KQ1 and KQ2 are excellent (with some flaws, below) but other issues in the methodology raise concerns about the overall applicability of the final document. These listed (especially 1 and 2) below are my main reason for listing the overall rating as only “fair” as they bring the whole report into question.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
Peer Reviewer #2	General	Unexplained or idiopathic cough (chronic) is a focal point of chronic cough and of this systematic evidence review for KQ1 and KQ2. However, the definition used in this effort for unexplained/idiopathic is not defined. What definition did the authors use to limit studies to "unexplained cough". The terms “unexplained chronic cough” (Page 11 of 196, 30 of 196) is used but what limitations were utilized to narrow studies into this area were not clearly delineated?	The final paragraph in the Patient Population section of the Introduction contains our working definitions for these constructs. “Patients with a chronic cough in whom an underlying etiology is not defined despite a thorough diagnostic workup are considered to have unexplained chronic cough. Patients in whom an underlying etiology has been identified, but in whom treatment fails to resolve the chronic cough, are considered to have refractory cough. How best to manage and treat patients with refractory cough and patients with unexplained chronic cough is uncertain and is the target of this systematic review.”
Peer Reviewer #2	General	KQ1: A key issue: Cough counting although a potential measure of cough severity is / can be inconsistently connected to quality of cough outcomes (quality of life) including cough induced incontinence, a common complaint in women. Assuming cough counting as a useful tool a priori and including in the measurement tools creates a flawed basic assumption in the efforts to garner evidence and develop of conclusions for KQ1.	Given the lack of a gold standard and in response to several reviewers’ comments, we have reworked the analysis of KQ1. Specifically we now use the following overall framework for our report: “For KQ 1 we considered the three dimensions of (1) cough frequency,

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			(2) cough severity (which might include quantity and characteristics of sputum, difficulty of expectoration, dyspnea, between cough sensations, or pain), and (3) cough-specific quality of life (QOL). While cough frequency is a unidimensional measure (although it is sometimes broken down into daytime and nighttime cough frequency), we considered cough severity and cough-specific QOL to be separate (and often multidimensional) dimensions of cough. Most of the standardized questionnaires included in this report measured aspects of both of these dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL together to be "severity/QOL" instruments. Within this report, we did not identify any validated instruments which focused purely on cough severity. We sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. For cough frequency, we evaluated validity by concurrence with measures of other constructs (e.g., cough severity, cough-specific QOL, tussigenic challenge (or cough reflex sensitivity), and exhaled nitrous oxide), and we assessed reliability using inter-method reliability (e.g., manual cough counts versus electronic recording device cough counts) and test-retest reliability. For severity/QOL instruments, we evaluated validity by looking at concurrence with

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			measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability, as well as internal consistency. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough.
Peer Reviewer #2	General	Inclusion / exclusion criteria (page 12 of 196, and 33 of 196): invasive respiratory tract instrumentation. Bronchoscopy is an invasive diagnostic tool in cough. Were patients with bronchoscopy as part of their evaluation included or excluded. Would be explicit regarding this specific tool/instrumentation.	This exclusion criterion refers to patients with cough resulting from invasive respiratory tract instrumentation. Bronchoscopy as a diagnostic tool for chronic cough would not preclude article inclusion. We have clarified this wording.

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Peer Reviewer #3	General	I realise this is a horrendous task accumulating all the relevant data but there does seem to be quite a lot of errors that jumped out at me in the tables describing the studies. The numbers of patients +/- controls seem to be dealt with in different ways and there are quite a lot of studies I was aware of, not included. For example, Table 5: Study Characteristics a) Birring 200832 did not use video recordings, included only 15 patients in evaluation of cough monitor, data was presented on 50 others but without evaluation b) Dicpinigaitis 200646 only 100 chronic cough patients in this study, not 671. c) Missing References (off the top of my head) i) A Kelsall, S Decalmer, K. McGuiness, A. Woodcock, J.A. Smith. Sex differences and predictors of objective cough frequency in chronic cough. Thorax. 2009 May;64 (5):393-8 ii) J.A. Smith, E.C. Hambleton, A.M. Jones, M.E. Dodd, A.K. Webb and A. Woodcock. Objective Measurement of Cough during Pulmonary Exacerbations in Adults with Cystic Fibrosis. Thorax 2006 May; 61(5):425-9 iii) Ashley Woodcock, Robbie L. McLeod, Jonathan Sadeh, Jaclyn A Smith. The Efficacy of a NOP1 Agonist (SCH 486757) in Sub-Acute Cough. Lung 2010 Jan;188 Suppl 1:S47-52 iv) Munyard P, Busst C, Logan-Sinclair R, Bush A. A new device for ambulatory cough recording Pediatr Pulmonol. 1994 Sep;18(3):178-86 v) Zihlif N, Paraskakis E, Lex C, Van de Pohl LA, Bush A. Correlation between cough frequency and airway inflammation in children with primary ciliary dyskinesia. Pediatr Pulmonol. 2005 Jun;39(6):551-7. vi) Li AM, Lex C, Zacharasiewicz A, Wong E, Erin E, Hansel T, Wilson NM, Bush A. Cough frequency in children with stable asthma: correlation with lung function, exhaled nitric oxide, and sputum eosinophil count. Thorax. 2003 Nov;58(11):974-8. vii) Vizel E, Yigla M, Goryachev Y, Dekel E, Felis V, Levi H, Kroin I, Godfrey S, Gavriely N. Validation of an ambulatory cough detection and counting application using voluntary cough under different conditions. Cough. 2010 May 27;6:3. viii) Leconte S, Liistro G, Lebecque P and Degryse JM. The objective assessment of cough frequency: accuracy of the LR102 device. Cough 2011, 7:11	We thank the reviewer for their careful revew of the report. We have revised tables and corrected data as suggsted. In addition, we have reviewed potential omissions from the literature base with the following determinations. Note that studies focusing on patients with cystic fibrosis were excluded. Kelsall reviewed and included. Smith reviwed and included. Woodcock reviwed and included. Munyard reviwed and included Zihlif reviewed and included. Li et al excluded for population not having cough or chronic cough Vizel et al excluded because patients were healthy subjects without cough LeConte et al included after updating literature search

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Peer Reviewer #3	General	I find the statement that electronic cough monitoring devices overall are accurate rather sweeping and would not agree. Many have been inadequately validated and so it's difficult to really comment on their performance and I think we still have a lot of work to do to really understand how best to represent performance.	We now clarify that electronic recording devices are accurate for assessing cough frequency, but they show variable correlation with instruments that measure other dimensions of cough
Peer Reviewer #3	General	The comments about Visual Analogue Scales are rather harsh in my view. Whilst specific studies haven't set out to validate cough VAS, many have included them when assessing QoL and objective monitoring and therefore there is quite a lot of data showing how they correlate with other measures. Such studies suggest to me that VAS measures still perform better than many other subjective scales.	Several reviewers have commented on the usefulness of VAS scores despite lack of data regarding validity for these tools. We have taken this into consideration in our revision of the chapter related to KQ1.
Peer Reviewer #3	General	Description of the studies suggests none was an RCT, but the table includes an RCT of codeine therapy of mine.	The revised "Description of Included Studies" section for KQ2 states, "Thirty-three of the 48 studies were parallel-group RCTs, and 12 were randomized crossover studies."
Peer Reviewer #3	General	Validity: I think the authors need to be careful suggesting that if cough recorders and human report similar counts that this means devices are highly valid. Counts may be similar, but this can occur as a consequence a number of missed coughs being counteracted by the number of false positives. Studies rarely report the extent to which human counters and the recorders have identified the exact same events.	This point is well appreciated and the discussion of electronic recording devices has been amended to reflect this possible weakness in assessing validity of these tools.
Peer Reviewer #3	General	I found the terminology throughout confusing, as sometimes the same cough counting system would be referred to as an electronic recorder, sometimes as a cough count. The reader is left uncertain as to whether the system being described is automated in some way or not.	We have reviewed and clarified the tables and text.
Peer Reviewer #3	General	In addition to the point made about validating cough recorders in laboratory conditions is an important one, but equally important is that many investigators only validate over short time periods when the device is planned to be used over 24hrs.	This point is well appreciated and the discussion of electronic recording devices has been amended to reflect this.

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Peer Reviewer #3	General	Some of the nuances of the differences between these studies that make them difficult to compare seem to have been lost. For example several cough monitor studies quantify coughing different ways. Also the Farqui 2011 study mainly uses a manual counting technique following filtering of the sounds files. This methodology has not to my knowledge been validated at all, but it is the results of this that are compared with other measures of cough. The results using the HACC are then only reported for 10 patients and compared to full 24hr human counts. The results suggest half the coughs are missed by the HACC.	We have reviewed the techniques used and comparisons made between the various electronic recording devices to ensure appropriate conclusions have been reached.
Peer Reviewer #3	General	It is suggested that none of the devices are available commercially but the Karmelsonix device described in Vizel et al (2010) is to my knowledge for sale, but missing from the list of publications.	The suggested study was reviewed and excluded as the population studied was healthy subjects without cough.
Peer Reviewer #3	General	Table 10. In Kelsall et al 2011 as well as cross-sectional correlations between cough counts and VAS (night plus day) we also showed no correlation between change in cough VAS and change in cough count suggesting responsiveness may be poor.	Data regarding responsiveness added. Thank you for calling this to our attention.
Peer Reviewer #3	General	Table 11: I am surprised the RCT of codeine in patient with COPD and cough was not included here as other studies of cough in COPD are listed.	We thank the reviewer for calling attention to this study. Although it was found in our orginal search it was was incorrectly excluded. We have now included this study after re-evaluation both for its evaluation of a nonspecific therapy for unresponsive cough and for its comparison of cough assessment tools.
Peer Reviewer #3	General	The key questions are appropriate and well defined however I have some major concerns about errors in the summary tables, missing publications and failure to appreciate some of the nuances in the different methodology used between studies, especially in cough monitoring, which is my main area of expertise.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
Peer Reviewer #4	General	Overall Quality: Fair well written, but data is quite fragmentary	We have revised the document to more clearly present the data.

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Peer Reviewer #4	General	This document suffers greatly from heterogeneity (in patients and treatments for KQ2) and lack of strong literature support. It is well-put together and represents an incredible amount of work and citation reviews. The material on KQ1 is thorough with recent literature. However, particularly with KQ2, any comments of recommendation are barely significant and always couched with terms of caution for interpretations. It is unclear exactly how this document is expected to be utilized. There is such variation in the patients in the included studies that a clinician will have great difficulty applying anything useful from it. In the KQ2 parts, much of the data is old and some of the medications are not even available in the US (which is interesting but it doesn¹t help a clinician with a coughing patient.) It would have been more helpful to someone using this document to have a broader discussion of other causes of cough, so that they could really get to the group of patients this document addresses.	A guideline exists from ACCP regarding diagnosing and treating various etiologies of cough. Our task for this systematic review was to evaluate treatments used specifically for unexplained or refractory cough. We share the reviewer's frustration regarding the lack of useful data to conduct a thorough comparative effectiveness review.
Peer Reviewer #4	General	Figure A/Figure 1, for example, includes "others", but doesn¹t address issues of poor airway protection with swallowing, environmental tobacco smoke exposure, psychogenic/stress/habit cough, tics, tracheomalacia, pertussis, etc. It would be helpful to caregivers to expand this area a significant amount, even if it is not the focus of the project.	The main focus of this report was to include studies that focused on unexplained or refractory cough. It was not in the scope of this report to evaluate diagnosis or treatment for other less common causes of cough although we understand how this information could be useful for clinicians and caregivers and may be a worthwhile subject for a subsequent report.
Peer Reviewer #4	General	It is amazing that, given the significance of cough in American healthcare (well-described), that the studies and data are so bad in addressing the assessment and especially care issues.	Again, we agree with the reviewer's frustration regarding the lack of data.
Peer Reviewer #4	General	Discussion of KQ1 little discussion of responsiveness measures it may be that the data is just lacking, but it seems that the ability to assess change in symptoms accurately is crucial.	We have revised our discussion of cough measurement tools with more focus on responsiveness of cough measurement tools. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough. .

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Peer Reviewer #4	General	ES-6: lines 24-26 grouping opiates with protussive mucolytics doesn¹t seem to make sense and didn¹t seem to appear in the later body of the report.	This categorzaition has been corrected
Peer Reviewer #4	General	Table 11 and Tables 18-21 (all graded as “insufficient SOE”) show the grim nature of the data addressing these issues. One could well ask “if the data is this bad, why is it worth nearly 200 pages?”	Despite the lack of good-quality data, we have attempted to present the existing state of the literature as fully as possible.
Peer Reviewer #4	General	I don¹t have specific suggestions for individual sections of the report they are well written and generally clear. They are certainly comprehensive. The report can¹t create new findings or significance where there isn¹t any.	Thank you
TEP #1	General	This paper is a meta-analysis studying the comparative value of tools for assessing cough and the comparative effectiveness of different treatments. The authors seek to address 1) comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough, and 2) the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough. The authors have a very nice Figure A which describes the role of their study questions in the overall process of cough management. The report is generally very well-written and is exhaustive in the description of the approach.	Thank you
TEP #1	General	While the details may be important for governmental agencies that seek to direct funding toward future needed research, the mere length of the document compromises it's significance to the practicing clinician. "The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives," but this document is also not appropriate for the layman consumer. Nevertheless, the scientific rigor in this meta-analysis is appropriate and the conclusions are sound.	Thank you

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TEP #1	General	There is an additional concern about the findings in light of the targeted key questions. The paper addresses survey instruments for key question 1, and the role of cough suppression therapy for key question 2. While "non-specific" treatments for chronic cough are important, I would value more of a targeted approach at diagnosing and treating the root causes of the chronic cough. (Figure C actually supercedes these non-specific treatments to include antibiotics, antihistamines, bronchodilators and corticosteroids, which are used to treat a "specific" etiology of the cough, however the text does not discuss their impact on non-specific treatments). The danger to the primary care physician and layman consumer is that there is little priority in diagnosing the cause of the cough, but rather it is ok to treat the manifestation of the disease (ie: a cough may be caused by a post-obstructive pneumonia resulting from bronchogenic carcinoma—should the priority be to measure the severity of the qough KQ1 or just suppress it KQ2?).	We agree that a review of the diagnostic work-up and treatment of specific etiologies of cough is an important topic but non-specific treatment was the scope as developed for this review. We have added wording to clarify this for the reader.
TEP #1	General	With these thoughts in mind, the paper should be more specifically targeting an appropriate audience (perhaps by changing the stated goals in the Executive Summary).	The intended audience for the AHRQ report is diverse and includes stakeholder of all types in addition to clinicians and researchers. We have therefore chosen to not limit the target audience by specifically listing for whom the report might be useful/appropriate
TEP #1	General	Overall, this is an excellent paper, and I appreciate the opportunity to add my thoughts to help expand it's relevance . The authors met their stated goals, but the broader vision should be addressed in the abstract and conclusion.	A guideline from the ACCP already exists outlining appropriate diagnosis and management of various cough etiologies. To that end, the intent of this report was to evaluate literature looking at nonspecific therapies and their potential usefulness in patients who cannot be easily diagnosed or treated and to evaluate the tools that may be helpful in assessing cough. We have attempted to highlight the implications of our findings for both clinicians and policy makers in our discussion.
TEP #2	General	The paper is very well written and relatively comprehensive. However it can be improved in its consistency in and there are areas that require adjustments for accuracy and context of cough.	Thank you

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TEP #2	General – Abstract	Abstract (with references to body of article) 1. It should be clearly stated the LCQ is for adults. Also the para 2 of the results section should state that the recommendations are in adults and the actual data should be inserted ie the effect size. Many people only read the abstract so it is essential that these are clear.	The Abstract has been updated to clarify these issues.
TEP #2	General – Executive Summary	Page ES-10: see comment 2 [immediately] above.	As above, the executive summary has been updated to reflect the changes requested.
TEP #2	General	The question about diary scores is arguably inaccurate. Change in diary scores have been related to change in objective cough counts. While the references have been inserted in adults (pg 45), the data relating change in diary cards vs change in cough sensitivity and objective cough counts have not been documented in the manuscript. That published in children has been completely omitted where these single point cross sectional correlations and two point studies (ie change b/w different measures) have been published. Although some the papers are in the included studies references, data within the papers have not been included in table 10 for eg. Further, surely the changes in measurements represent responsiveness of the diaries and other outcome measures.	We have restructured KQ1, clarifying our methods and the structure of our report with the following text: "For KQ 1 we considered the three dimensions of (1) cough frequency, (2) cough severity (which might include quantity and characteristics of sputum, difficulty of expectoration, dyspnea, between cough sensations, or pain), and (3) cough-specific quality of life (QOL). While cough frequency is a unidimensional measure (although it is sometimes broken down into daytime and nighttime cough frequency), we considered cough severity and cough-specific QOL to be separate (and often multidimensional) dimensions of cough. Most of the standardized questionnaires included in this report measured aspects of both of these dimensions. Therefore, for the purpose of this report, we considered instruments that measured both severity and QOL together to be "severity/QOL" instruments. Within this report, we did not identify any validated instruments which focused purely on cough severity. We sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. For cough

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			frequency, we evaluated validity by concurrence with measures of other constructs (e.g., cough severity, cough-specific QOL, tussigenic challenge (or cough reflex sensitivity), and exhaled nitrous oxide), and we assessed reliability using inter-method reliability (e.g., manual cough counts versus electronic recording device cough counts) and test-retest reliability. For severity/QOL instruments, we evaluated validity by looking at concurrence with measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability, as well as internal consistency. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough.".
TEP #2	General	A key missing context about measurements is that they are not interchangeable and this has not been appreciated. Just as in asthma, asthma control is not interchangeable to various lung function (such as FeNO or spirometry indices), a similar concept exists in almost all conditions. Thus objective cough measures cannot be equated to cough diaries (day to day measures) which is also different to QOL. In any disease, QOL cannot substitute other outcome measures.	As described above, we have restructured KQ1 to focus on: ability to assess cough frequency or cough severity/ quality of life. However, despite notable differences in various measures of cough, the assessment of concurrent validity, reliability, and responsiveness require analysis of the association of different measures.
TEP #3	General	While it is clear that the authors spent a considerable amount of time reviewing and analyzing data and writing this report, this reviewer finds the report lacking in a variety of ways. FIRSTLY, while the target population and key questions are appropriate and explicitly stated, the synthesis of information regarding K1 is flawed by a) assuming that cough counting should be used to assess the quality of cough specific health related	Thank you for the helpful suggestions. As described above, we have restructured KQ1 to focus on the ability of cough measurement tools to 1) assess frequency, or 2) assess severity/impact on life,. For each of these measures we sought to measure the validity, reliability, and

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		quality of life instruments and by b) failing to define unexplained or refractory cough to help them address K2. Both issues should have been resolved before the project began. Did the authors ask the advice of content experts before beginning this project? It does not appear that they did.	responsiveness. For cough frequency, we evaluated validity by concurrence with measures of other constructs; we assessed reliability by assessing inter-method reliability (e.g., manual cough counts versus electronic recording device cough counts), and test-retest reliability. For cough severity/impact instruments, we evaluated validity by looking at concurrence with measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability as well as internal consistency. We evaluated responsiveness of both frequency and severity/impact measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough. We had an operational definition of unexplained or refractory cough which we developed with input from Key Informants and a Technical Expert Panel. We report on the extent to which studies met this definition, but nearly all studies failed to either meet this definition in practice or failed to report adequate information about study population or conduct to assess the study with regards to the definition. Specifically we note: "Finally, the evidence exploring the effectiveness of treatments in patients with truly unexplained cough was minimal. We considered the vast majority of study populations to have unresponsive chronic cough. Only

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			three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough. Interestingly, therapy in each of these studies was associated with a reduction in cough severity, suggesting that chronic unexplained cough can respond to nonspecific therapies aimed at the symptom and not the underlying etiology." This peer review draft is an opportunity to get further feedback regarding both the quality and volume of literature as well as the execution of the systematic review and analysis.
TEP #3	General	If I had been asked, I would have reminded the Duke group that health related quality of life measurement tools assess a patient's perception of the impact of cough on MULTIPLE domains of his/her life (e.g., physical function or psychosocial state) and not just cough frequency. Those of us working in the cough field know that a patient may have a low cough frequency but pass out or wet their pants with 1 out of 5 coughs in a day while another patient may cough 100 times and not have it happen once. Also, patients can frequently cough from cigarette smoking but not even be aware that they are coughing because it doesn't bother themor they accept the consquence (French CT, et al. Evaluation of a cough-specific quality of life questionnaire. CHEST 2002; 121: 1123-1131). Therefore, the frequency of cough is not the most important thing to monitor; and cough counting should not have been used as a surrogate "gold standard" to assess the accuracy or usefulness of the cough health related quality of life questionnaires. What should have been used? Because a gold standard does not exist and never will, the standard(s) that should have been used were outstanding psychometric testing to establish Validity (content, concurrent, contruct), reliability (internal consistency and repeatability, and responsiveness to change and determining the minimal important difference; and comparisons to other valid and reliable health related quality instruments. While	We agree that there is currently no gold standard for assessing cough. As the reviewer acknowledges, we did seek to assess not only concurrent validity with cough frequency but also reliability, responsiveness to change and comparisons with other instruments. We have also restructured the analysis and discussion of cough assessment tools to focus on their respective abilities to assess cough frequency or severity/quality of life. Specifically: "We sought to measure the validity, reliability, and responsiveness of various instruments used to assess each of these dimensions. For cough frequency, we evaluated validity by concurrence with measures of other constructs (e.g., cough severity, cough-specific QOL, tussigenic challenge (or cough reflex

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		the authors did attempt to also do the latter, it did not appear to be their major focus and it was done in an inconsistent and incomplete way. (I will provide specific examples of this below).	sensitivity), and exhaled nitrous oxide), and we assessed reliability using inter-method reliability (e.g., manual cough counts versus electronic recording device cough counts) and test-retest reliability. For severity/QOL instruments, we evaluated validity by looking at concurrence with measures of other constructs including cough frequency, quality of life, and tussigenic challenge findings. We assessed reliability by test-retest reliability, as well as internal consistency. We evaluated responsiveness of both frequency and severity/QOL measures by reporting data on changes in these measures over time associated with treatment (or no treatment) of cough symptoms or the underlying etiology of cough."
TEP #3	General	If I had been asked, I would have advised the Duke group to define unexplained (idiopathic) or refractory cough as the ACCP 2006 Guideline did. Had they done this, they then could have commented upon how well the literature addressed the issue of intervention fidelity in diagnosing the unexplained cough group and assessed how frequently the unexplained cough group was possibly unexplained because certain tests or certain treatments were never done. They then could have restricted the populations in their K2 analysis to those who met the definition of unexplained cough by the ACCP 2006 definition. Because of these 2 issues, the document, as it stands, is not clinically meaningful.	The systematic review process included content experts at both the key informant and technical expert panel levels. Unfortunately, during our systematic review we found almost no studies that conducted and described an evaluation that would satisfy the ACCP 2006 Guideline recommendation. Had we restricted the review to such studies, the report would be of little use because of lack of data and this is now clarified within the report. Specifically we note: "Finally, the evidence exploring the effectiveness of treatments in patients with truly unexplained cough was minimal. We considered the vast majority of study populations to have unresponsive chronic cough. Only

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			three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough. Interestingly, therapy in each of these studies was associated with a reduction in cough severity, suggesting that chronic unexplained cough can respond to nonspecific therapies aimed at the symptom and not the underlying etiology." We describe in the KQ2 Study Characteristics table the best available information included in the study to make the determination regarding the cough etiology. In the column labeled Cough/Population Description we describe how studies characterized the selection criteria related to the symptom of cough, and in the column labeled Included Disease we describe etiologies that were related to cough etiology, or note if cough was unexplained. We considered the vast majority of study populations to have unresponsive chronic cough. Only three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough (Morice, 2007, Ribeiro, 2007, and Yousaf, 2010). These studies are noted as such in the KQ2 Study Characteristics Table.

Commentator & Affiliation	Section	Comment	Response
TEP #3	General	SECONDLY, the manuscript reflects (a) an incomplete literature review, (b) a failure to complete the job it set out to do, (c) inaccurate and incomplete reporting of results, and (d) failure to adequately proof read the submitted work. When these issues arise in a manuscript, it leaves the reader with the perception that the project was not carried out in a trustworthy manner. a. The following articles that used the CQLQ and were not excluded by the authors do NOT appear in Table 7: 1) French, CT, et al. CHEST 2004; 125: 482-488 (while some of the patients had been previously reported, there were additional patients added to the cohort in this paper). 2) French CT, et al. CHEST 2005; 127: 1991-1998. None of the data in this report had been previously reporteed. 3) Jeyakumar A, et al. Laryngoscope 2006; 116: 2108-2112. 4) Field SK, et al. Can Respir J 2009; 16: 49-54. 50 5) Field SK, et al. CHEST 2009; 136: 1021-1028 (asked different question as the preceding article) 6) Shaheen NJ, et al. Alimentary Pharmacol Ther 2011; 33: 225-234. 7) Irwin RS, et al. CHEST 2002; 121: 1132-1140. (In this article, the authors used the Adverse Cough Outcome Survey (ACOS) that was the first generation of the CQLQ [the differences being only one more item and binary choices for subjects]) (The Duke group did not appear to be aware that all of the ACOS publications related to the CQLQ puiblications and VAS scores were also used but not mentioned in Table 10 where data on VAS scoring was tabulated. The Field studies mentioned above had VAS data also but these were not mentioned in Table 10 either.) 8) Novitsky YW, et al. Surg Endosc 2002; 16: 567-571 (The ACOS [1st generation CQLQ] was again used here and compared with the Sickness Impact Profile.) Because I was able to easily find these additional studies that the Duke group failed to find or chose not to use, I must assume that other reviewers will find others that were left out.	All of the listed citations were found in our original search and either included in our report or described in Appendix D with a reason for exclusion if they progressed to the full-text screening stage. Citations which were excluded at the abstract level are not explicitly listed. We have however gone back through the suggested citations and considered their inclusion anew: -French 2004 was reviewed and excluded for no outcomes of interest. -French 2005 was excluded for no outcomes of interest: shows CQLQ is sensitive to differences between acute and chronic coughers. -Jeyakumar 2006 is a RCT comparison of amitriptyline vs. codeine/guaifenesin in a population with chronic cough “resulting from postviral vagal neuropathy”. Because this is a known and specific etiology, and amitriptylline is not used for non-specific cough, this article was excluded. – - Irwin 2002 was reviewed and included -Field 2009a was reviewed and excluded for no interventions or outcomes of interest.. -Field 2009b was reviewed and included. -Shaheen 2011 was reviewed and included- --Novitsky 2002 was reviewed and included.

Commentator & Affiliation	Section	Comment	Response
TEP #3	General – Figure	b. In figure A. Analytic Framework, the authors state that they will assess the literature on tussigenic challenge and exhaled nitric oxide. They do not appear to have done so and those of us working in the field had hoped that this would be covered.	We had hoped to evaluate how well tussigenic challenge agreed with other measures such as cough frequency, symptom scores and QoL measures. Unfortunately, during the systematic review we found little or no data in the study population of interest. Similarly, we included nitric oxide as a search term in the literature search strategy; however, the studies we found about nitric oxide didn't fit the key questions. Nitric oxide seemed to be used in diagnostic role as a way of identifying patient with cough-variant asthma or NAEB. We now clarify both these points in the text.
TEP #3	General	In table 6, the authors are incorrect in stating that the CQLQ was performed in a population derived of "adults with acute or chronic smoking-related cough." The control group was smokers who had a cough but did not complain of cough. Also, there is no acknowledgement or understanding in Table 6 that the ACOS was basically the CQLQ with one more item (29 versus 28). The additional item was removed in the CQLQ because it was redundant. With respect to the CQLQ, Table 14 is inaccurate and incomplete. While there have been multiple studies that assessed the repeatability of the CQLQ, the table reports that none exist. Moreover, the Cronbach's alpha scores for the total CQLQ scores was higher than the range that is given and the range that is given is inaccurately assessed as low. Lastly, a range is reported for the MID that inaccurately combines an MID assessed retrospectively with one assessed propectively. In this very important paper (Fletcher KE, et al. J Clin Epidemiol 2010; 63: 1123-1131), the authors empirically show for the first time that a retrospective global rating of change scale has recall bias and the authors wanted the prospectively assessed MID to be used, not a range.	As suggested, we have modified our description of the control group to clarify. In addition, we have modified our discussion to clarify the relationship between the ACOS and CQLQ. Based on the reviewers concerns, we have also further searched for studies that meet our inclusion criteria and that report on the repeatability of CQLQ. We have reexamined the cited Cronbach's alpha statistic, and reexamined the Fletcher data acknowledging the CQLQ as the underlying QoL measure, and the Punum Ladder as merely the method for determining the MID.

Commentator & Affiliation	Section	Comment	Response
TEP #3	General	Issues that surfaced during my review that fall under the category of failure to adequately proof read the submitted work include the following: 1) incorrectly saying on page 19 of 107 under Research Gaps that the CQLQ is the tool for children because it is an adult health related quality of life tool. This is done again on page 20 of 107 and elsehwere. Did you mean the PC-QOL? 2) incorrectly stating on page 47 of 107 that the Global Rating of Change Scale is a health related quality of life questionnaire. It isn't. It assesses change and has recall bias in determining the MID of such instruments. See the Fletcher paper. 3) On page 47, incorrectly listing the Punum Ladder and not the CQLQ as a health related quality of life instrument. The Punum ladder was developed as a tool to PROSPECTIVELY assess the MID of health related quality of life measures such as the CQLQ. On page 48, the Duke group has incorrectly stated that the responsiveness of the Punum ladder was studied rather than the CQLQ. 4) On page 74, I was able to determine that citations and references were not correct for the following statement: "....cough severity, and/or quality of life (LCQ) in five of the studies (92, 95, 104, 106, 114). References 92, 95, 104, and 114 could not have used the LCQ because these articles were published in 1956, 1981, 1983, and 1971 before the LCQ was published. Because of reviewer fatigue, I was not inclined to check all the references for accuracy. What I found makes me wonder about the accuracy of the other citations.	1. We have corrected this error also pointed out by reviewer #2 2-3. We have corrected this mischaracterization of GRCS and Punum Ladder. 4. The cited studies are accurate. Each of the 5 studies cited reported that opiates were more effective than placebo for one or more of the named outcomes. We did not mean to imply that they all used the LCQ. We have reworded this sentence to make this clearer.
TEP #4	General	KQ1: I see that there are few pediatric data supporting the use of any measurement device or survey for evaluating chronic cough in children. The Leicester Cough Questionnaire (LCQ) has been determined to be valid with internal consistency and reliability in the adult population. It would be appropriate to explicitly state whether this questionnaire has also been studied in children as well the strength of data supporting its use in children.	We have looked to see if any data regarding the LCQ in children and report findings. Unfortunately, no studies evaluated its measurement accuracy in the pediatric population.

Commentator & Affiliation	Section	Comment	Response
TEP #4	General	KQ2: This is more troublesome. I note that arbitrarily, chronic cough in adults and children over the age of 14 years has been defined as greater than 8 weeks in duration and under 14 years as under 4 weeks in duration. I recognize that there are few studies in children and that the four week cut off has been chosen as a matter of convenience. I also note that the largest study in children to date by Marchant and colleagues used 3 weeks as a cutoff. In this pediatric study greater than 20% of children with chronic cough of 3 or more weeks duration had spontaneous resolution before the initiation of investigations or therapy suggesting that a 3 or4 week cutoff is inappropriately short. I also note that the presumed mechanism of action of a number of the pharmacologic agents is arbitrary and not supported by either physiologic or pharmacologic data. As but one example, medications such as guaifenesin, listed as an expectorant, do not have data supporting this. This may bias the interpretation of smooth ease data.	The thresholds used in the systematic review were based on the nominated topic and discussions with the key informants and technical expert panel. As the reviewer points out, a shorter duration of cough threshold will reduce specificity for a cough that is chronic, meaning that spontaneous resolution (of acute cough) is more likely. When supportive physiologic or pharmacologic data were lacking, the mechanisms of action for certain medications was stated as the commonly believed mechanism of action. Label indications were used to maximize reader understanding.
TEP #4	General	In general it is disappointing but not entirely surprising that there are so few high quality data that it will be difficult to make recommendations.	We agree that the lack of data regarding the treatment of chronic cough in children is disappointing – and highlights the need for future research
Public Reviewer #1	General	I do not have enough knowledge of the published literature to comment concerns about published studies that were not included or incomplete/inaccurate data.	Thank you
Public Reviewer #2 – Surinder Birring, King's College, London	General	I am commenting specifically on quality of life and electronic cough counting devices. It is clear that the reviewers have spent considerable time researching this area. However, without prior expertise in cough, I feel that the reviewers were not in a position to come to some of the conclusions that they did. I wholly agree with them that it is difficult to establish the accuracy of particularly the electronic cough monitoring devices because so little is published, and key data has been omitted from the publications available. The reviewers are left to make comparisons between different cough assessment tools. I am not sure they appreciate that all of these cough assessment tools, VAS, Quality of Life and Cough Monitoring assess different aspects of cough severity, and are all important in their own right. The lack of a good correlation between two tools does not imply that either one of them are inaccurate.	This point is appreciated. However, the aim of the report was to provide a comparative effectiveness review and so efforts were made to do so, even with limited data.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 – Surinder Birring, King's College, Londond	General	I am surprised by some of the conclusions in Table A (page ES10) that summarises the performance characteristics of the Quality of Life Questionnaire. The CQLQ is deemed to have an insufficient strength of evidence for internal consistency but, at the same time, a respectable Cronbach alpha co-efficient is stated. Again, for the CLQ, insufficient strength of evidence is stated for repeatability but, in the original description of the CQLQ, a respectable intraclass correlation co-efficient was reported. I believe that the comments about the CQLQ's internal consistency and repeatability are not justified. The review of cough electronic cough monitoring devices, although very detailed, is unhelpful for the development of a clinical guideline. I sympathise with the reviewers because, through no fault of their own, it is extremely difficult to establish which cough monitors have been developed, how they work and the performance characteristics. The review of electronic cough monitors does not reflect the current state of affairs for available monitors for adult patient use: 1. Cough COUNT: sound and chest wall movement-based, automated, accuracy largely unknown. 2. Leicester cough monitor: sound-based, semi-automated (very minor operator-input required, 10min). 3. VitaloJAK: sound-based, manual counting with the assistance of customised software to reduce quiet (non-cough) periods. Certainly, for the latter 2 monitors, there is data to support their use in clinical practice and clinical trials. Their output is remarkably similar and consistent. Lastly, Visual Analogue Scales are reported very unfavourably. I appreciate the fact that validation experiments have not been reported explicitly. However, one can find data regarding relationship with other cough parameters, repeatability and responsiveness within several studies. They are a useful resource, widely used and accepted.	We have reviewed our data regarding QOL questionnaires with more emphasis on the following domains: ability to measure cough frequency and cough severity, recognizing that QOL does not always correlate well with cough frequency and thus other measures besides cough counting (i.e. other QOL scores, VAS scales) may be more effective tools to evaluate the effectiveness of QOL questionnaires. We also thank the reviewer for the information provided regarding electronic cough monitors. We have reflected this in the updated version of the report. Finally, several reviewers have commented on the usefulness of VAS scores despite lack of data regarding validity for these tools. We have taken this into consideration in our revision of the chapter related to KQ1.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3	General	I had hoped that the methodology as set out at the outset would be robust and yet I agree that despite this there have been a number of omissions form the literature. I was particularly struck by the number of papers listed in the appendices that have been excluded. I think these will need to be carefully reviewed by hand – In particular I could not see good the reason why a number listed under 'study population does not have cough (KQ1) or chronic cough (KQ2)'. Good examples of this would be: 1.leaving out a study by Chaudhuri et al (JACI 2004) which addressed the use of inhaled corticosteroids in adults with persistent cough. 2.Only one study by Dicpinigaitis despite quite a few studies on capsaicin challenge testing in the literature 3. Study by Doherty MJ et al on the capsaicin challenge testing in patients with cough due to lung fibrosis. 4. A number of clinical trials of cough treatment in children undertaken by Ian Paul seem to have been omitted. 5. A number of non pharmacological interventions do not seem to have been covered (e.g. speech pathology intervention/laparoscopic fundoplication). Some of this may be because some of the search restrictions for KQ1 and KQ2 set out need to be relaxed. These are just a few examples and I am quite certain that other reviewers will identify many more missing from the review Another point I wish to make relates to over quality of medical writing – this has been done with no sense of the clinical context. The abstract is poorly constructed. Examples of this include the use of the term 'electronic recording' to describe studies on ambulatory cough recording and a statement that says 'opioid anti-tussives demonstrated the most promise for managing chronic cough'. I am sure what they meant to say was that the studies available to date suggest they have some efficacy in the treatment of cough but nobody with a clinical understanding of chronic cough would say they 'are promising' treatments. I think it would have been preferable if the Duke team had help more than just one brief T/C with the technical review panel at the outset. I also feel that someone with a clinical interest in cough and a good knowledge of systematic review should be invited to assist Duke with the interpretation and write up of the analysis.	We have reviewed the cited exclusions to ensure there were no inappropriate exclusions to the literature base. The decision was made to consider corticosteroids as a nonspecific treatment for chronic cough if the patients did not suffer from cough due to an etiology for which corticosteroids is considered a targeted therapy (i.e. COPD). To this end, Chaudhuri et al was included after re-review. In addition, the two studies by Doherty wereincluded. A third study by Doherty was identified but excluded because population consisted of healthy vounteers without cough. Thrity-seven studies by Dicpinigaitis were identified in our initial literature search. Almost all were excluded for one of the following reasons 1) not an evaluation study 2) outcome of focus was cough sensitivity reflex which was not one of our outcomes of interest or 3) evaluated an intervention that was no an intervention of intereest (i.e. baclofen) Seven studies by Paul were identified in our initial literature search. All but one were excluded due to population being healhty subjects without cough or patients with acute cough in studies evaluating treatment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #4	General	My main concern is the document's primary focus to serve as a 1) reference for clinicians, 2) resource for the lay public, and 3) guide areas in need for further research and funding. The lengthy document does none of these. If they tightened their focus to examining the levels of evidence for subjective analysis of cough severity, as well as symptomatic-based cough suppression, then the document is a starting point, noting Richard's concerns. The broader goals they stated (and I outlined above) are not met. Clinicians need a concise document that addresses all components of cough, with a complete differential diagnosis and treatment plan. The lay public probably doesn't care much about subjective cough severity measures, and needs more of a basic understanding in a concise document than presented here. And I'm hopeful that the federal government would not rely on this document for potential lapses to fund, as I believe research in more important areas of cough physiology deserve attention and funding.	A guideline already exists which provides an algorithm for diagnosing and treating cough for which an etiology can be determined (previously published by the ACCP). Our systematic review focus is on unexplained or unresponsive chronic cough for which there unfortunately there is little data to create a useful guideline for clinicians. Our other task was to compile data on currently employed cough measurement tools in an attempt to compare the effectiveness of these tools in assessing cough. Again, there is little data to completely address the comparative effectiveness of these tools. We are hopeful that the information in the report will at least be helpful in highlighting what data is available.
Public Reviewer #5	General	I did read over these documents. Since I am new to the committee, I have no specific comments to add beyond what has been previously stated.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #6 – Peter Gibson	General	there is no mention of the role of systematic assessment and treatment of chronic cough, eg the irwin approach. some assesment of this is required, even if you say no rcts available. where there are trials that use a systematic approach, eg Wei ref 122, you seem to reduce these to a simple rct comparison and dont mention the actual trial purpose and intervention which was sequential therapy. this is a limitation of your methodological framework there is a big gap in not addressing people with explained cough. this is the majority of people seeking medical help for cough. there is no mention i could find as to why this was not in scope. there is no mention of the role of systematic assessment and treatment of chronic cough, eg the Irwin approach. some assesment of this is required, even if you say no rcts available	The focus of KQ1 was of the assessment of cough and of KQ2 was the non-specific therapies for cough. We did not review articles that suggested an algorithm approach to the diagnostic assessment of cough or that tested treatment of underlying diagnoses of chronic cough. A guideline already exists which provides an algorithm for diagnosing and treating cough for which an etiology can be determined (previously published by the ACCP). Our task for this AHRQ-commissioned systematic review was specifically to address this other population of patients with unexplained or refractory cough.
Public Reviewer #7 – Martha Dewey Bergren, National Assocation of School Nurses	General	It is disappointing and concerning that no studies of currently available treatments for chronic cough in children were identified. Managing children with a chronic cough is a frequent and significant challenge to nurses who work with children, especially school aged students. The cough not only disturbs the attentiveness, comfort and sleep of the child who is coughing, it also disturbs other students in the classroom and the teachers. Chronic cough is a common problem that interferes with learning for the child with the cough and for those in the classroom with the child. “Children are … an important and distinct population of interest for the management of unexplained or refractory chronic cough.” Yet, the lack of studies and due to the risk of adverse events, parents and child caretakers, including schools and day care providers are left without approved medications. A similar dearth of information was noted on non-pharmological interventions for cough in children. Non-pharmalogical interventions are a priority in setting where parents are not available for consent for medications. The systematic review highlights the gaps in the literature and provides evidence for increased study of chronic cough in adolescents and children of all ages.	We agree with your disappointment in the lack of pediatric data.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	Excellent overview of the problem, presentation of the questions, and analytic framework b. p 2: Population: It would be useful to readers to know how common [3]chronic cough, no identifiable cause or non response to specific treatment[2] is in for example, a primary care population or specialty care clinics (see Chung 2008, Lancet [3]prevalence, pathogenesis, and causes of chronic cough[2]). If you feel that there are no pertinent descriptive studies or estimates available, feel free to say this. Or give an estimate of the prevalence of chronic cough with a comment about the percentage of cases that are without identifiable cause, if known.	We have added in data concerning how common chronic cough is within the US as suggested
Peer Reviewer #2	Introduction	Introduction: Page 27 of 196: focus on United States is important given the audience for AHRQ but what is the prevalence of unexplained cough world wide? Addition of this information or delineation of the what is known outside of US would increase the value of the introduction and the paper overall.	Text regarding the prevalence of chronic cough worldwide has been added. Given the focus of the AHRQ EPC systematic reviews on the US population, we excluded therapies that are not available in the US but studies from countries outside the US were included if the studied therapy was available in the US.
Peer Reviewer #3	Introduction	I have no major problems with the introduction and background	Thank you
Peer Reviewer #4	Introduction	Sets the foundation, but, again, the patient reports are very heterogeneous.	Thank you
TEP #1	Introduction	Introduction: well-written, excellent.	Thank you
TEP #2	Introduction	Introduction: OK	Thank you
TEP #3	Introduction	Because this manuscript covers cough issues in a global manner, the authors should try to find out how commonly patients in other countries, not just the US, seek medical care because of cough. I know that similar data exist in Australia. This background information should be added to Executive Summary as well as Background in full manuscript.	The primary audience of the AHRQ EPC Program are stakeholders within the US and therefore this is the focus of this report.
TEP #3	Introduction	Benzonatate and guaifenesin and acetycysteine are mentioned as if they have been shown to work but not clear if they have a role to play.	We have reworded these statements to acknowledge uncertainty regarding their efficacy/effectiveness.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Introduction	On page 10 and in Executive Summary, it is not clear what you mean by invasive respiratory tract instrumention. You should not eliminate studies in which bronchoscopy was performed.	This exclusion criterion refers to the clinical setting in which cough is observed. The review was not tasked to assess the ability of treatments to reduce cough during bronchoscopy (or associated with anesthetic agents used during procedures). We did not however specifically exclude studies that happened to use bronchoscopy as a diagnostic procedure as part of the evaluation of cough etiology. We have reworded to make this distinction clearer.
TEP #4	Introduction	see general comments above	Thank you
Peer Reviewer #1	Methods	Comprehensive and logical search strategy, reasonable inclusion/exclusion criteria.	Thank you
Peer Reviewer #1	Methods	Outcomes definitions reasonable and reflect weakness of the underlying literature.	Thank you
Peer Reviewer #1	Methods	Statistical method appropriate. Please mention the cutoffs that you applied for statistical heterogeneity (I2 and p-value for Q) and what you did if the two statistics had differing conclusions.	Methods section clarified as suggested.
Peer Reviewer #1	Methods	Please mention the summary effect size used.	Methods section clarified as suggested.
Peer Reviewer #2	Methods	Methods: Yes to first and second other than explained above. Also, see above re bronchoscopy. Also see above re the critical term definition of "unexplained cough" and how that impacts the search strategy. Statistical methods are quite solid and well explained.	Thank you – these comments have been address above
Peer Reviewer #3	Methods	Whilst the methods, inclusion and exclusion criteria seem reasonable and are clearly stated, a number of pertinent studies have been missed and it not clear to me why.	We have reviewed all studies that have been cited as missing from the report. All studies were identified in the original literature search but were excluded at the abstract or full-text level. We have reviewed these exclusions to evaluate whether this was an appropriate determination and have included those studies in the revised report that were appropriate for inclusion.
Peer Reviewer #4	Methods	Appropriate	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #1	Methods	Methods: the approach to the study is well-defined, and the search strategies exhaustinve and thorough. I'm not a statistician and can therefore not comment on those methods.	Thank you
TEP #2	Methods	The date when the searchers were performed needs to be inserted in the document, the abstract, the exec summary and within the body of the document.	Will have added search dates; note that these dates now reflect the updated search performed during the peer review period.
TEP #2	Methods	Summary of findings or evidence table should be consistent- for eg table A was created when there were 4 or more studies yet the same criteria was not used for all the other summary tables. For a systematic review, the same criteria must be used. In Cochrane reviews a SoF table is generated as long as there is data and arguably, it should be the same as why was n=4 studies chosen?	We have added additional instruments in to the summary evidence table where data is available
TEP #2	Methods	The question of refractory coughing with a known etiology- a definition would be helpful or some sort of description ie if the underlying condition is suboptimally treated, should it still be refractory cough? For eg, if a patient had chronic bronchitis and was treated as if he/she had asthma and cough is still present, theoretically it is not refractory cough. How would optimal Rx be defined for the different conditions? I suspect it will not be possible to fully elucidate these characteristics but there needs to be some sort of discussion and a caveat clearly stated in the summary and within text.	We had an operational definition that was used in assessing the articles for inclusion and exclusion which we now include in the methods section. Specifically we note that “Patients with a chronic cough in whom an underlying etiology is not defined despite a thorough diagnostic workup are considered to have unexplained chronic cough. Patients in whom an underlying etiology has been identified, but in whom treatment fails to resolve the chronic cough, are considered to have refractory cough.” Unfortunately, few studies actually documented a process for evaluating and treating chronic cough that would satisfy, for example, the ACCP guidelines. We therefore aimed to describe the study populations, diagnostic evaluation and treatment trials that were performed. We have augmented the discussion on this limitation of the literature in the discussion.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Methods	Because multiple studies were missed, it is not clear if your search strategy was correct. I had no difficulty finding papers you missed using OVID.	The studies cited were found by literature searching, but excluded. We have reviewed these studies and where noted included their findings in the final report.
TEP #3	Methods	As I mentioned in my general comments, I am concerned with how you decided to analyze the data and how you went about finding subjects with unexplained cough.	The final paragraph in the Patient Population section of the Introduction contains our working definitions for these constructs. "Patients with a chronic cough in whom an underlying etiology is not defined despite a thorough diagnostic workup are considered to have unexplained chronic cough. Patients in whom an underlying etiology has been identified, but in whom treatment fails to resolve the chronic cough, are considered to have refractory cough. How best to manage and treat patients with refractory cough and patients with unexplained chronic cough is uncertain and is the target of this systematic review." Unfortunately much of the literature did not provide sufficient detail to ensure that patients clearly had unexplained cough. Specifically we note: "Finally, the evidence exploring the effectiveness of treatments in patients with truly unexplained cough was minimal. We considered the vast majority of study populations to have unresponsive chronic cough. Only three studies, including one of morphine, were clearly in patients with unexplained cough and required subjects to have gone through a diagnostic evaluation to exclude most causes of cough. Interestingly, therapy in each of these studies was

Commentator & Affiliation	Section	Comment	Response
			associated with a reduction in cough severity, suggesting that chronic unexplained cough can respond to nonspecific therapies aimed at the symptom and not the underlying etiology."
TEP #3	Methods	You do not appear to have critically reviewed if there are limitations to the health related quality of life instruments. For example, you appear to think that the LCQ is the best adult health related quality of life instrument even though it and the CQLQ performed similarly overall in the only 2 head to head comparisons (Polley L, et al. CHEST 2008; 134: 295-302 and Kalpaklioglu AF, et al. Ann Allergy Asthma Immunol 2005; 94: 581-585). Moreover, you do not even mention that the CQLQ may have distinct advantages over the LCQ in its ability to capture sex differences in chronic cough because the LCQ, unlike the CQLQ, does not have an item that assesses the most important side effect from cough in women, that being urinary incontinence (This was brought out by Kelsall A, et al in Thorax 2009; 64: 393-398.) Moreover, only the CQLQ of any health related quality of life questionnaire in existence has had its MID assessed prospectively. All others have had their MIDs assessed by retrospective tools that are subject to recall bias.	We have modified our report and now state: "The CQLQ, which includes six domains, has been shown to correlate with the LCQ, both of which appear to be better at assessing the impact of chronic cough than the SF-36. The CQLQ offers an advantage over the LCQ in its ability to capture sex differences in chronic cough because the LCQ, unlike the CQLQ, does not have an item that assesses urinary incontinence as an important side effect of cough."
TEP #4	Methods	see general comments above	Thank you
Public Reviewer #1	Methods	[ES] there is a typo on page 14 - in the second line under the Data Synthesis heading, the sentence beginning For KQ1,…	This typo has been corrected
Public Reviewer #1	Methods	[ES] I do not understand why they combined opiate antitussive drugs and mucolytic protussive drugs in the KQ2 analysis (page 14 - Data Synthesis and it is mentioned in other places as well). I don't think this affected the results so it may not make a difference but the rationale was not clear.	We have removed that sentence
Peer Reviewer #1	Results	The key messages are well distilled and clearly described.	Thank you
Peer Reviewer #1	Results	For the three quantitative syntheses, please mention the summary effect size that you used (e.g. standardized mean difference or ??) (p 61). Also, with each summary effect size, state the number of studies included and which studies these were (p 61). Were there 11 studies in each of the three syntheses? This is what the second paragraph under quantitative synthesis implies though I suspect that this was not the case.	Results section clarified as suggested.
Peer Reviewer #1	Results	Figure 4: Relabel the title to reflect that this figure is a summary of the 3 syntheses. Label the x-axis.	Figure 4 has been updated as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	Briefly describe the studies included in the quantitative synthesis. It would useful to know how cough severity was measured in these studies and the study methods (p 61).	We have inserted the additional details as suggested
Peer Reviewer #2	Results	Results: Yes to these questions: very well written and outlined document. But with the critical points regarding above concerns #1 and #2...this impacts study selection overall. Tables and figures are quite clear and descriptive as are the appendices.	Thank you – these comments have been address above
Peer Reviewer #3	Results	The results section is presented in sufficient detail however the tables contain multiple errors in describing the studies, a number of studies are missing (at least 8 just off the top of my head) and inconsitencies in the language used are likely to confuse the reader. I have uploaded a word file with specific points). I also think the authors have failed to understand the differences between some of the cough monitoring studies and how they were performed. This is however a complex and difficult task and must be extremely challenging for those without specific expertise in the field.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
Peer Reviewer #4	Results	In some ways this seems excessive, given how bad the available data are.	Please see response to similar concern from other reviewers in terms of the benefit of a systematic review given scarce data.
TEP #1	Results	Results: The results are vey nicely presented in figure, table and text form.	Thank you
TEP #2	Results	Results: In addition to the points 3 and 4 under general comments: I am surprised that only a single paper was identified on corticosteroids. Examples of missing RCTs are below and there are more.If such studies are excluded- a reason for their exclusion needs to be given for transparency purposes. A table of some of the key papers most would think fulfil the criteria would be helpful (as done in Cochranereviews) Boulet LP et al, AJRCCM 2004;149:482-489 (study inclusion criteria was4 weeks but the adults were coughing from 0.25 years to 20 years). This paper was referenced in Œno outcome of interest- but to me it¹s incorrect). R. Chaudhuri, A. D. McMahon, L. J. Thomson, K. J. Macleod, C. P.McSharry, E. Livingston, A. McKay, and N. C. Thomson. Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. J Allergy Clin Immunol 113 (6):1063-1070, 2004.	We included the suggested Chaudhuri citation in our revised report. The Boulet study was reviewed but excluded based on the patients not having unexplained cough (1/2 of the patients had postnasal discharge and so beclomethasone could be seen as a targeted therapy for underlying etiology)

Commentator & Affiliation	Section	Comment	Response
TEP #3	Results	Please see my concerns expressed in the general comments section.	Thank you
TEP #4	Results	see general comments above	Thank you
Peer Reviewer #1	Discussion/ Conclusion	Major findings are clearly stated.	Thank you
Peer Reviewer #1	Discussion/ Conclusion	Limitations of the review and studies adequately described.	Thank you
Peer Reviewer #1	Discussion/ Conclusion	Excellent discussion of findings in relationship to what is already known.	Thank you
Peer Reviewer #1	Discussion/ Conclusion	The investigators mention that they omitted studies of acute cough.Given the paucity of studies in children with chronic cough, the authors note that future reviews on chronic cough in children may want to include studies of acute cough.	We agree that the paucity of studies in children was disappointing and that potentially an expansion of the inclusion criteria related to pediatric studies might be justified for future reviews
Peer Reviewer #1	Discussion/ Conclusion	Applicability (p 86). Consider editing this section to better highlight the most important threats to applicability. For example, country of origin is mention early but does not seem to be the greatest threat to applicability.	We agree with the reviewer's suggestion and have reorganized the section.
Peer Reviewer #1	Discussion/ Conclusion	Earlier the authors mentioned that only one study actually required a work-up for a specific cause of the cough prior to enrollment in the study so while this review is more applicable that previous studies as this review excluded acute cough, highlight this problem that very few (one?) actually specifically targeted the population of interest. This point is lost in this discussion of applicability.	We have removed this sentence and clarified
Peer Reviewer #1	Discussion/ Conclusion	p 89 Research Gaps (lines 42-43): The authors state "Chronic cough is a common health problem that is associated with significant health complications and reduction in health-related quality of life." Please support this statement in the document somewhere and/or temper this comment (use "may") or omit. For example, based on reading this report, I do now know how common chronic cough is, what the significant health complications are, nor the nature of the reduction in health-related quality of life.	We have modified the wording as suggested
Peer Reviewer #2	Discussion/ Conclusion	Discussion/ Conclusion: Yes to question 1 re major findings. Limitations outlined but concerns as noted re "#1 and #2" above.	Thank you – these comments have been address above
Peer Reviewer #2	Discussion/Conclusion	Future research needs well outlined.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Discussion/ Conclusion	The implications of the major findings are clearly stated but I would not agree with some of them. This is in part due to the missing literature but also I have the sense the authors do not understand the priocesses of cough monitor validation and therefore are failing to see that most devices have been insufficiently validated. Therefore to suggest cough monitoring devices overall are accurate overall strikes me a sweeping statement and largely untrue. I would have concluded the opposite! Equally the comments on cough VAS are over harsh, many studies have found correlations between VAS and other cough measures suugesting some validity.	This point is well appreciated and we have amended our discussion of electronic recorders to reflect this possible weakness in assessing validity of these tools. Several reviewers have commented on the usefulness of VAS scores despite lack of data regarding validity for these tools. We have taken this into consideration in our revision of the chapter related to KQ1.
Peer Reviewer #4	Discussion/ Conclusion	The comments about identifying gaps in knowledge and the desperate need for new research are very true and probably the most useful and important part of the whole report.	Thank you
TEP #1	Discussion/ Conclusion	Discussion/ Conclusion: The discussion and conclusions are meaningful. Again, if the intent of the study was to generate clinically meaningful information for the practicing physician, then expanding the study to explore prioritization in working up the causes of chronic cough, determining the efficacy of diagnostic methods needed for those causes, and determining the comparitive efectiveness of treatments for those etiologies would be of more general interest.	Thank you for the comment – unfortunately the workup of causes of chronic cough is outside the scope of this comparative effectiveness review.
TEP #2	Discussion/ Conclusion	Discussion/ Conclusion: In addition to all point above: Pg EQ15, Research Gaps The suggestion that CQLQ should be tried in children depicts a lack of understanding of paediatric vs adult issues. The CQLQ is a self completed questionnaire (as all adult Q are). Those in paediatrics, are usually parent proxy (for young children who cannot report their QOL) or self completed (in a very different format to adult ones (for older children). Further the adult cough-QOL all contain questions not relevant to children such as wet my pants[1], soil my pants[1], I am concerned I have cancer[1] (these Q are in CQLQ). Incontinence are not relevant in young children and hence the suggestion of CQLQ for children is rather odd and should be removed in the exec summary as well as in the body of the article (eg pg 89).	We apoligize for the typo error. The CQLQ was erroneously referenced instead ot the PC-QOL. The Discussion/Conclusion and Executive Summary have been amended to correct these issues As described above, the body of the report related to KQ1 has been rewritten according to a new focus and these issues have also been addressed in the rewriting..

Commentator & Affiliation	Section	Comment	Response
TEP #2	Discussion/ Conclusion	Further, the PC-QOL has internal consistency (Cronbach alpha value of0.92) unlike what is stated (pg ES-8) and has been used in clinical studies showing it is more sensitive than generic QOL (Chest 2012: epub ahead Mar 29). It is possible that the search was performed before the study above was published and hence the importance of stating the search dates (point 1). This point should be removed in	This article was identified in our updated search and included in the KQ1 chapter. The discussion of PC-QOL has been updated as appropriatte.
TEP #2	Discussion/ Conclusion	While there is always room for improvement, the statement is not correct. In fact the paediatric studies were also conducted in controls (ie children without cough) which was not done in most adult studies and as stated above the related changes has been shown (ie two time point measurement as opposed to single time point). The PC-QOL has the repertoire of all the necessary requirements with minimal change, psychometric properties, effect size, use in various populations on cough, use in a RCT. What is missing is a child-completed cough specific QOL (as opposed to parent-proxy ones). To develop this, it has been done properly starting with focus groups on the target group (i.e. children) and not adults (which is the basis for CQLQ) and hence the suggestion of using CQLQ is scientifically flawed).	Revisions were made to the Discussion to reflect the appropriateness of certain QOL questionnaires in the adult versus the pediatric populations.
TEP #3	Discussion/ Conclusion	Unless the concerns that I have expressed are adequately addressed in a revised manuscript, this review by the Duke group will not be useful. Too much important literature has been left out and the synthesis and reporting of data are inadequate.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
TEP #4	Discussion/ Conclusion	see general comments above	Thank you
Peer Reviewer #1	Clarity/Usability	Yes, report well structured and organized and clearly presented. Authors make reasonable conclusions for policy and practice design based on the extremely limited evidence.	Thank you
Peer Reviewer #2	Clarity/Usability	Clarity and Usability: Yes to the first to questions. Regarding last question, the overall study is in doubt for reasons outlined above and therefore utilizing to inform policy decisions in doubt.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
Peer Reviewer #3	Clarity/Usability	The report is well structure and organised, the main points are clearly stated but I would suggest a number are incorrect based on the existing evidence. They need revising after inclusion of additional literature and a more careful study of the data especially around cough monitoring.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
Peer Reviewer #4	Clarity/Usability	It is well structured. However, due to the heterogeneity of the patients and the marginal conclusions, I'm not sure how a clinician will be able to effectively use the report to improve the care they give. I would urge expanding the discussion related to Figure A/Figure 1.	This point is appreciated. However, the aim of the report was to provide a comparative effectiveness review and so efforts were made to do so, even with limited data.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Clarity/Usability	Clarity and Usability: The report is well structured and organized, and the main points clearly presented. Although the conclusions define lapses in the data which may be used to inform policy (such as directing clinical research funds), it's clinical value is limited by 1) length of the document, 2) inaccessibility to the layman consumer population, and 3) lack of focus on including a meaningful approach to the diagnosis and treatment of underlying etiologies (rhinologic, pulmonary, esophageal, other) contributing to the cough. The study therefore has limited impact on practice decisions.	Please note that AHRQ's Eisenberg Center will be tasked with creating consumer-specific products summarizing the report. In addition, we feel an systematic review of the literature regarding non-specific therapies of cough is valuable given these therapies are used broadly. The optimal approach to the diagnosis and management of underlying etiologies is also important and was the topic of a prior systematic review and guideline but is not the focus of this review.
TEP #1	Clarity/Usability	Further study on the role of heightened sensory receptors, and more targeted pharmacotherapy would be a praiseworthy goal for additional funding (although the document presented here would not inspire such an effort).	The scope of this report was not to address targeted pharmacotherapy, but we agree that any additional research that could potentially improve patient outcomes would be beneficial. Note suggestions for new topics needing systematic review can be nominated through the AHRQ website
TEP #2	Clarity/Usability	Clarity and Usability: The report is structured but lacks some clarity and transparency. Unless, changed, this is limited given the above points.	Revisions were made to the text as suggested to improve clarity.
TEP #3	Clarity/Usability	While the report is well structured and organized, the plan behind the analysis is flawed, the literature has not been carefully or completely reviewed. It appears that experts in content were not asked for their advice before the authors embarked upon how they were going to analyze the data.	We thank the reviewer for their helpful comments and hope that they feel that the revised report addresses their concerns.
TEP #4	Clarity/Usability	see general comments above	Thank you