Evidence-based Practice Center Systematic Review Protocol

Project Title: Assessment and Management of Chronic Cough

Amendment Date(s):

Amendment 1 – October 4, 2012

(Amendment Details – see Section VII)

I. Background and Objectives for the Systematic Review

In the United States, cough is the most common complaint for which patients seek medical attention and is the second most common reason for a general medical examination—accounting for over 26 million office visits in the U.S. annually.[1] Often cough results from an acute self-limited viral upper respiratory tract infection; however, there are multiple causes of cough beyond the common cold, including both respiratory tract and nonrespiratory tract–related etiologies. Cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older is considered to be chronic. Such chronic cough is responsible for up to 38 percent of pulmonary outpatient visits.[2,3]

Although cough is a troublesome symptom that causes discomfort to patients, it serves a potentially beneficial purpose: it clears the airways of excessive mucus, irritants, or abnormal substances such as edema fluid or pus. But while cough may serve a useful function, it can also lead to a variety of problems, including exhaustion (57%), feeling self-conscious (55%), insomnia (45%), changes in life-style (45%), musculoskeletal pain (45%), hoarseness (43%), excessive perspiration (42%), and urinary incontinence (39%).[4] The purpose of this review is to evaluate the effectiveness of instruments to evaluate cough and the comparative effectiveness of treatments for the symptom of cough for patients with either refractory or unexplained cough.

Patient Population

Across all ages, there are many causes of chronic cough, of which more than one may affect any particular patient. The three most common causes of chronic cough in adult nonsmokers for which patients seek medical attention are upper airway cough syndrome (UACS, formerly known as postnasal drip syndrome), asthma, and gastroesophageal reflux disease (GERD).[2,3,5-7] Several prospective studies[2,3,6-9] suggest that chronic cough is due to multiple causes 18 to 62 percent of the time. Even in patients for whom the underlying cause of cough has been identified and treated, the symptom of cough may persist and cause continued distress.

In patients with no identifiable cause of cough (unexplained or idiopathic) or no response to specific treatment (unresponsive, refractory, or intractable), chronic cough poses a particularly challenging problem. For adult patients in whom a specific cause of chronic cough is not easily identified, the American College of Chest Physicians (ACCP) 2006 guidelines recommend an empiric approach to diagnosis and treatment. This approach begins with a trial of an antihistamine (first generation) and decongestant (for presumed UACS), followed by an assessment for cough-variant asthma by bronchoprovocation challenge (BPC) followed by a trial of asthma treatment or, if BPC is not available, an empiric trial of antiasthma therapy. If the BPC

is negative or an empiric trial of antiasthma treatment is ineffective, then an assessment for nonasthmatic eosinophilic bronchitis (NAEB) is recommended, by induced sputum test for eosinophils. If this test is positive, or if it cannot be performed, then a trial of inhaled corticosteroids is recommended. Finally, if the induced sputum for eosinophils is negative or a trial of corticosteroids is negative, then empiric treatment for GERD is recommended. 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 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 cough is uncertain and is the target of this systematic review.

Current Treatment

The diagnosis and management of cough has been the subject of several guideline efforts,[10-12] two aimed at assessment of cough in adults[10,11] and one focused on children.[12] Guidelines from the ACCP, last updated in 2006, are the most comprehensive resource and will be the subject of a future update.[11] According to these guidelines, initial clinical evaluation is aimed at determining the cause or underlying etiology of cough based on history, physical examination, and, if the cough is chronic, chest x-ray. Several measurement methods exist to evaluate cough severity, including health-related quality of life (HRQOL) instruments, visual analog scales, cough counts (using real-time wearable computerized equipment), and tussigenic challenge. These methods, however, have had limited acceptance within the broader clinical community, and their current use and subsequent impact on clinical decisionmaking and patient outcomes is small.

If treatment of the underlying etiology fails to resolve the cough, or if no cause can be identified, then the cough may be treated symptomatically (Table 1). In the majority of cases, symptomatic treatment consists of antitussive therapy to decrease the frequency and severity of the cough. Antitussive treatments vary in mechanism of action—nonspecific antitussives such as dextromethorphan and codeine appear to act in the brain stem to reduce the cough reflex. Other nonspecific antitussives, such as benzonatate, act to anesthetize respiratory passages and thus reduce the stimulus to cough. Other agents aim to decrease the volume of respiratory tract secretions and thus the stimulus and need to cough. These agents are also used to treat certain common underlying etiologies (e.g., UACS, NAEB) and include antihistamines, corticosteroids, antibiotics, decongestants, and mast cell stabilizers. Nonpharmacological antitussives are few but may include, for example, honey. Recently, speech therapy interventions have been used to treat chronic cough in patients suspected of hypersensitivity of upper airways.[13]

In a limited number of situations where the cough provides a useful function (such as in bronchiectasis, pneumonia, or atelectasis), protussive therapy may be used in an attempt to increase cough effectiveness without increasing its frequency. Protussive treatments aim to change the characteristics of mucus in such a way that it can be cleared more effectively by mucociliary action or cough. Such effective clearing can subsequently lessen the severity and frequency of a patient's cough. Protussive pharmacologic agents include expectorants, mucolytics, and mucus-modifying agents. Examples of these include guaifenesin, hypertonic saline, and acetylcysteine. In addition, physical maneuvers such as chest physical therapy, flutter

valves, or pneumatic jackets may be used, especially in patients with respiratory muscle weakness.

Table 1. Commonly used therapies available in the U.S. for symptomatic treatment of chronic cough

Broad Category	Medication/Therapy Class	Therapy Name
Nonspecific pharmacologic antitussives (cough suppressants)	Anesthetics	Benzonatate
	Opiates	Codeine, hydrocodone
	Other	Dextromethorphan
Nonpharmacologic antitussives	Foods	Honey, tea, lemon, liquor
	Psychological	Cognitive behavioral therapy
	Alternative	Acupuncture, tai chi, yoga, meditation
	Multidimensional	Speech therapy
Protussives	Expectorants	Guaifenesin
	Mucolytic or mucus modifying	Acetylcysteine, dornase alfa inhaled
Nonpharmacologic protussives	Physical	Chest physical therapy

Rationale for Evidence Review

Measurement methods to formally evaluate cough severity have had limited acceptance within the broader clinical community. If accurate and reproducible measurement methods can be identified, this may lead to more widespread use of more clinically relevant outcomes in clinical research studies. Such a measurement method could also be clinically useful to practicing clinicians when evaluating the efficacy of chosen treatments or assessing the severity of a patient's chronic cough. A recent systematic review of pharmacological and nonpharmacological interventions for cough in adults with respiratory and nonrespiratory diseases evaluated 75 randomized controlled trials (RCTs) published through 2009. This review, mainly in patients with asthma and chronic obstructive pulmonary disease, found that cough was measured in less than one-fourth of the studies.[14] The authors concluded that cough should be measured as the primary outcome with the use of validated methods that consider all dimensions of the cough experience. Given that the review found a lack of clarity in the assessment of cough, an analysis of existing evidence is necessary to begin the process of describing, implementing, and/or developing cough-related health outcome measurement techniques.

Managing the symptom of chronic cough, regardless of whether the etiology is known, is a challenge to even the most experienced health care providers. Several RCTs have shown no effect or harmful effects of over-the-counter medications in children, while few have shown positive results for treatment alternatives. Duration of treatment, especially in asthmatic children, is not clearly specified in existing guidelines. The benefits of antihistamines in young children (primarily under 12 years of age) with chronic cough are also not clearly understood. Because of the risk of adverse events, the U.S. Food and Drug Administration (FDA) recommends that cough and cold medicines not be used for children under 6 years of age, and the industry has voluntarily withdrawn these medicines for children under 2 years of age. Similarly, in adults,

RCTs for commonly used antitussive and protussive treatments are relatively few and sometimes inconclusive. A review that covers recent trials using newer agents and methodologies may add significantly to the evidence base for guiding treatment.

II. The Key Questions

The draft key questions (KQs) developed during topic refinement were available for public comment from September 26, 2011, to October 24, 2011. The comments received helped to elaborate populations and outcomes of interest but did not lead to substantive changes in the KQs or methods.

The KQs are:

KQ 1. In adults and adolescents (≥14 years of age) and children (<14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough?

KQ 2. In adults and adolescents (≥14 years of age) and children (<14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?

(a) In patients with unexplained chronic cough
(b) In patients with refractory cough with a known underlying etiology

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

Populations

- KQ 1: Adults and adolescents (≥ 14 years of age) and children (< 14 years of age) presenting with cough. (Note that the population in KQ 1 is not limited to patients with unexplained or refractory chronic cough as it is in KQ 2. While the majority of the clinical use of these instruments will be in patients with unidentified or refractory cough, the underlying cause of the cough should not make the instrument perform differently in its ability to assess the patient's cough severity/frequency; therefore getting rid of studies which include patients with known etiology would reduce the applicable evidence unnecessarily.)
- KQ 2: Adults and adolescents (≥ 14 years of age) and children (< 14 years of age)
  - With unexplained chronic cough defined as a cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older and without a known underlying etiology
  - With refractory chronic cough with a known underlying etiology defined as a cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older. The underlying etiology for the cough is known but treatment for the etiology has not eliminated the cough.
  - Subgroups of potential interest include:
    - Age (the elderly [over 65 years] children under 6 years of age, children under 2 years of age, infants); note that these subgroups will allow us to specifically explore populations for which different treatments or comparators apply (for

example, differing FDA recommendations)
- Pregnant women
- Women
- Underlying etiologies (asthma, GERD, upper airway cough syndrome, tobacco use, ACE inhibitor use, pulmonary infection, bronchitis, cystic fibrosis, others)
- Immunocompromised patients
- Patients with a history of substance abuse

Interventions

- KQ 1: Qualitative and quantitative instruments used to assess chronic cough. Instruments include, but are not limited to, generic and cough-specific health-related quality-of-life instruments; visual analog scales; objective cough counting; tussigenic challenge; and exhaled nitric oxide.
- KQ 2: Nonspecific symptomatic treatment of cough with antitussive and protussive medications. Antitussive treatments include opiates (codeine, hydrocodone), dextromethorphan, and respiratory anesthetics (benzonatate). Protussive treatments include expectorants (guaifenesin) and mucolytic or mucus-modifying agents (acetylcysteine, dornase alfa inhaled). In addition, alternate nondrug treatment (e.g., chest physiotherapy, herbal remedies, aroma therapy, acupuncture, humidifiers, medicated vapors, alcohol, honey, speech therapy) will be considered.

Comparators

- KQ 1: Other instruments. Proposed reference standard will be cough counts
- KQ 2: All of the above-listed interventions compared both within class and across classes

Outcome measures

- KQ 1:
  - Diagnostic accuracy:
    - Sensitivity
    - Specificity
    - Positive and negative predictive values
    - Reliability: interrater and intrarater reliability, test-retest reliability
    - Responsiveness: standardized response mean and responsiveness index
    - Feasibility: response rate, time required
    - Validity: test validity measures including patient-reported improvement/worsening, treating provider global impression, complementary clinical data
  - Therapeutic efficacy:
    - Change in clinical practice
    - Aid to provider decision making
    - Aid to patient decision making
  - Patient centered outcomes:
    - Acceptability to the patient
    - General and cough-specific health-related quality of life

        - Chest pain
        - Depression
        - Anxiety
- KQ 2:
    - Patient centered outcomes:
        - Cough symptoms
        - Cough severity
        - Cough frequency
        - Complications related to coughing
        - Functional status
        - General and cough-specific health-related quality of life
        - Health care utilization and costs
    - Adverse effects of antitussive, protussive, and nonpharmacologic interventions including, but not limited to:
        - Sleep disturbance
        - Allergic reaction
        - Drowsiness
        - Headache
        - Chest pain
        - Dizziness
        - Rash

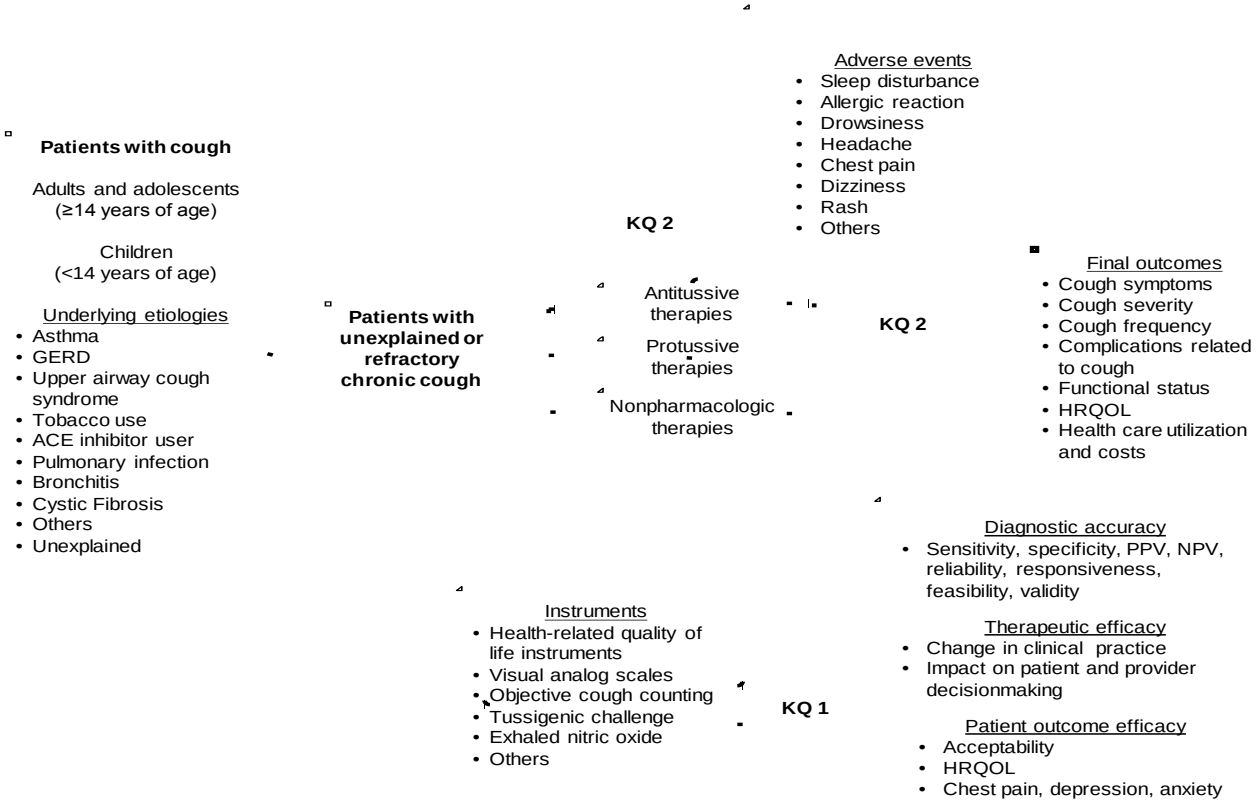
Timing

Since our patient population is patients with chronic cough, included studies will need to define the patient population to be those with a cough that lasts more than 4 weeks in children younger than 14 years of age or more than 8 weeks in adolescents and adults 14 years of age and older. Timing of followup is not limited.

Setting

Both inpatient and outpatient settings

III. Analytic Framework



Abbreviations: ACE = angiotensin-converting enzyme; GERD = gastroesophageal reflux disease; HRQOL = health-related quality of life; KQ = key question; NPV = negative predictive value; PPV = positive predictive value

IV. Methods

In developing this comprehensive review, we will apply the rules of evidence and evaluation of strength of evidence recommended by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the *Methods Guide*).[15] We will solicit feedback regarding conduct of the work (such as development of search strategies and identifying outcomes of key importance) from the Task Order Officer and the Technical Expert Panel. We will follow the methodology recommended to the Evidence-based Practice Centers for literature search strategies, inclusion/exclusion of studies in our review, abstract screening, data abstraction and management, assessment of methodological quality of individual studies, data synthesis, and grading of evidence for each KQ.

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

We will use the following inclusion/exclusion criteria for studies in our systematic review. Specific medications and devices are listed in Appendix 1.

Table 2. Inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Populations	• Humans • KQ 1: Patients with cough (any duration) • KQ 2: o Patients with chronic cough (persisting 4 weeks if <14 years of age or 8 weeks if ≥14 years of age, or as stated by study authors) o Patients with unexplained or idiopathic, unresponsive, refractory, intractable, or uncertain chronic cough • Subgroups of potential interest include: o Age (the elderly, children under 6 years of age, children under 2 years of age) o Pregnant women o Women o Underlying etiologies (asthma, GERD, upper airway cough syndrome, tobacco use, ACE inhibitor use, pulmonary infection, bronchitis, cystic fibrosis, others) o Immunocompromised patients o Patients with a history of substance abuse	KQ 2: • Patients with chronic cough of known etiology undergoing specific therapy • Patients with invasive respiratory tract instrumentation (e.g., ventilator dependent, tracheostomy, endotracheal intubation)
Interventions	• KQ 1: Qualitative and quantitative instruments used to assess cough (e.g., general and cough-specific health-related quality-of-life instruments, visual analog scales, objective cough counting, tussigenic challenge, exhaled nitric oxide) • KQ 2: Nonspecific symptomatic treatment of cough with: o Antitussive medications such as opiates (codeine, hydrocodone), dextromethorphan, and respiratory anesthetics (benzonatate) o Protussive medications such as expectorants (guaifenesin) and mucolytic or mucus-modifying agents (acetylcysteine, dornase alfa inhaled) o Alternate non-drug treatments such as chest physiotherapy, herbal remedies, aroma therapy, acupuncture, humidifiers, medicated vapors, alcohol, honey, speech therapy	None

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Comparators	• KQ 1 (instruments): Other instruments; the proposed reference standard will be cough counts • KQ 2 (interventions): All of the above-listed interventions compared both within class and across classes	None
Outcomes	• KQ 1: Study assesses an outcome of interest: o Diagnostic accuracy (e.g., sensitivity, specificity, positive predictive value, negative predictive value, validity, reliability, responsiveness, feasibility) o Therapeutic efficacy (e.g., change in clinical practice, impact on patient or provider decisionmaking) o Patient outcome efficacy (e.g., acceptability, quality of life, chest pain, depression, or anxiety) • KQ 2: Study assesses an outcome of interest: o Cough symptoms o Cough severity o Cough frequency o Complications related to coughing o Functional status o Health-related quality of life (generic or cough-specific) o Health care utilization and costs o Adverse effects of antitussive, protussive, and nonpharmacologic interventions including sleep disturbance, allergic reaction, drowsiness, headache, chest pain, dizziness, rash	KQ 2: Study assesses outcomes only using induced sputum (relevant only to patients with wet or productive cough) or bronchoprovocation challenge (measures hyperresponsiveness relevant to measuring lower airway reactivity to diagnose asthma)
Timing	• Timing of followup will not be limited[a] • Studies must define the patient population to be those with a cough that lasts more than 4 weeks in children <14 years of age or more than 8 weeks in adolescents and adults ≥14 years of age	None
Setting	Inpatient and outpatient	None
Study design	• KQ 1 (instruments): Evaluation studies • KQ 2 (interventions): Randomized trials, cohort studies • All sample sizes	• Not a clinical study (e.g., editorial, non–systematic review, letter to the editor, case series) • KQ 2: Case-control studies

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Publications	• English-language only • Peer-reviewed articles • Relevant systematic review, meta-analysis, or methods article (used for background only)	Given the high volume of literature available in English-language publications, the focus of our review on therapies actively used within the US, and the scope of our current key questions, non-English articles will be excluded[b]

[a]For all included studies, we will indicate the total number of patients enrolled and longest length (weeks or months) of followup if relevant.
[b]It is the opinion of the investigators that the resources required to translate non-English articles would not be justified by the low potential likelihood of identifying relevant data unavailable from English-language sources. We will monitor the number of articles excluded at the abstract stage for English language and determine whether this exclusion criterion should be revisited.
Abbreviation: KQ = key question

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

To identify the relevant published literature, we will search MEDLINE®, Embase®, and the Cochrane Database of Systematic Reviews. Where possible, we will use existing validated search filters (such as the Clinical Queries Filters in PubMed®). An experienced search librarian will guide all searches. Our proposed search strategy for PubMed is included in Appendix 2; this strategy will be adapted as necessary for use in the other databases. We will supplement the electronic searches with a manual search of citations from a set of key primary and review articles. The reference list for identified pivotal articles will be manually hand-searched and cross-referenced against our library, and additional manuscripts will be retrieved. All citations will be imported into an electronic database (EndNote X4). As a mechanism to ascertain publication bias, we will search ClinicalTrials.gov to identify completed but unpublished studies. While the draft report is under peer review, we will update the search and include any eligible studies determined either during that search or identified by peer or public reviewers in the final report. We will use several approaches to identifying relevant gray literature including a request for scientific information packets submitted to drug and device manufacturers listed in Appendix 1 and a search of U.S. FDA device registration studies and new drug applications. We will also search the gray literature of study registries and conference abstracts for relevant articles from completed studies. Gray literature databases will include ClinicalTrials.gov; metaRegister of Controlled Trials; ClinicalStudyResults.org; WHO: International Clinical Trials Registry Platform Search Portal; and ProQuest COS Conference Papers Index.

For MEDLINE, Embase, and the Cochrane Database of Systematic Reviews, two reviewers using prespecified inclusion/exclusion criteria will review titles and abstracts for potential relevance to the research questions. Articles included by either reviewer will undergo full-text screening. At the full-text screening stage, two independent reviewers must agree on a final inclusion/exclusion decision. Articles meeting eligibility criteria will be included for data abstraction. All results will be tracked in the DistillerSR data synthesis software program (Evidence Partners Inc., Manotick, ON, Canada).

C. Data Abstraction and Data Management

The research team will create data abstraction forms for the KQs that will be programmed in the DistillerSR software. Based on their clinical and methodological expertise, a pair of researchers will be assigned to abstract data from each of the eligible articles. One researcher will abstract the data, and the second will over-read the article and the accompanying abstraction to check for accuracy and completeness. Disagreements will be resolved by consensus or by obtaining a third reviewer's opinion if consensus cannot be reached. Guidance documents will be drafted and provided to the researchers to aid both reproducibility and standardization of data collection.

We will design the data abstraction forms for this project to collect the data required to evaluate the specified eligibility criteria for inclusion in this review, as well as demographic and other data needed for determining outcomes (intermediate, final, and adverse events outcomes). We will pay particular attention to describing the details of the treatment (e.g., pharmacotherapy dosing, methods of nonpharmacologic therapies), patient characteristics (e.g., underlying etiology of chronic cough, age of patient), and study design (e.g., RCT versus observational) that may be related to outcomes. In addition, we will describe comparators carefully as treatment standards may have changed during the study period. The safety outcomes will be framed to help identify adverse events, including those from drug therapies (sleep disturbance, allergic reaction, drowsiness, headache, chest pain, dizziness, rash) and those resulting from nonpharmacological therapies. Data necessary for assessing quality and applicability, as described in the *Methods Guide*,[15] will also be abstracted. Before they are used, abstraction-form templates will be pilot-tested with a sample of included articles to ensure that all relevant data elements are captured and that there is consistency/reproducibility between abstractors. Forms will be revised as necessary before full abstraction of all included articles.

D. Assessment of Methodological Quality of Individual Studies

We will assess the methodological quality, or risk of biases, for each individual study by using the assessment instruments detailed by AHRQ's *Methods Guide*.[15] Briefly, we will rate each study as being of good, fair, or poor quality based on its adherence to well-accepted standard methodologies (i.e., QUADAS-2[16] for studies of diagnostic accuracy and the Downs and Black methodologic quality assessment checklist[17] for intervention studies). For all studies, the overall study quality will be assessed as follows:

- **Good** (low risk of bias). These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a clear description of the population, setting, approaches, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair**. These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor** (high risk of bias). These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

The grading will be outcome specific such that a given study that analyzes its primary outcome well but did an incomplete analysis of a secondary outcome would be assigned a different quality grade for each of the two outcomes. Studies of different designs will be graded within the context of their respective designs. Thus, RCTs will be graded good, fair, or poor, and observational studies will separately be graded good, fair, or poor.

E. Data Synthesis

We will begin by summarizing key features of the included studies for each KQ. To the degree that data are available, we will abstract information on study design; patient characteristics; clinical settings; interventions; and intermediate, final, and adverse events outcomes.

We will then determine the feasibility of completing a quantitative synthesis (i.e., meta-analysis). Feasibility depends on the volume of relevant literature, conceptual homogeneity of the studies, and completeness of the reporting of results. When a meta-analysis is appropriate, we will use random-effects models to quantitatively synthesize the available evidence. We will test for heterogeneity using graphical displays and test statistics (Q and I^2 statistics), while recognizing that the ability of statistical methods to detect heterogeneity may be limited. For comparison, we will also perform fixed-effect meta-analyses. We will present summary estimates, standard errors, and confidence intervals. We anticipate that intervention effects may be heterogeneous. We hypothesize that the methodological quality of individual studies, study type, duration of chronic cough, age of the patient, the characteristics of the comparator, adherence to existing guidelines on workup of known etiologies, and patients' underlying clinical etiology will be associated with the intervention effects. If there are sufficient studies, we will perform subgroup analyses and/or meta-regression analyses to examine these hypotheses.

F. Grading the Evidence for Each Key Question

We will grade the strength of evidence for each outcome assessed; thus, a given study may be graded to be of different quality for two individual outcomes reported within that study. The strength of evidence will be assessed by using the approach described in the *Methods Guide*.[15,18] In brief, the approach requires assessment of four domains: risk of bias, consistency, directness, and precision. Additional domains are to be used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains will be considered qualitatively, and a summary rating of high, moderate, or low strength of evidence will be assigned after discussion by two reviewers. In some cases, high, moderate, or low ratings will be impossible or imprudent to make, for example, when no evidence is available or when evidence on the outcome is too weak, sparse, or inconsistent to permit any conclusion to be drawn. In these situations, a grade of insufficient will be assigned. This four-level rating scale consists of the following definitions:

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

G. Assessing Applicability

We will assess applicability across our key questions using the method described in the *Methods Guide*.[15,19] In brief, this latter method uses the PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) format as a way to organize information relevant to applicability. The most important issue with respect to applicability is whether the outcomes are different across studies that recruit different populations (e.g., age groups, exclusions for comorbidities) or use different methods to implement the interventions of interest; that is, important characteristics are those that affect baseline (control-group) rates of events, intervention-group rates of events, or both. We will use a checklist to guide the assessment of applicability. We will use these data to evaluate the applicability to clinical practice, paying special attention to study eligibility criteria, demographic features of the enrolled population in comparison to the target population, characteristics of the intervention used in comparison with care models currently in use, and clinical relevance and timing of the outcome measures. We will summarize issues of applicability qualitatively.

V. References

1. Centers for Disease Control and Prevention. National Ambulatory Medical Care Survey: 2008 Summary Tables. Available at: http://www.cdc.gov/nchs/ahcd.htm. Accessed November 29, 2011.
2. Irwin RS, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. Am Rev Respir Dis 1981;123(4 Pt 1):413-7. PMID: 7224353.
3. Irwin RS, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 1990;141(3):640-7. PMID: 2178528.
4. Irwin RS, Curley FJ. The treatment of cough. A comprehensive review. Chest 1991;99(6):1477-84. PMID: 2036833.
5. Holinger LD, Sanders AD. Chronic cough in infants and children: an update. Laryngoscope 1991;101(6 Pt 1):596-605. PMID: 2041439.

6. Pratter MR, Bartter T, Akers S, et al. An algorithmic approach to chronic cough. Ann Intern Med 1993;119(10):977-83. PMID: 8214994.

7. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest 1995;108(4):991-7. PMID: 7555175.

8. Mello CJ, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 1996;156(9):997-1003. PMID: 8624180.

9. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. Lancet 2008;371(9621):1364-74. PMID: 18424325.

10. Morice AH, Fontana GA, Belvisi MG, et al. ERS guidelines on the assessment of cough. Eur Respir J 2007;29(6):1256-76. PMID: 17540788.

11. Irwin RS, Baumann MH, Bolser DC, et al. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest 2006;129(1 Suppl):1S-23S. PMID: 16428686.

12. Finnish Medical Society Duodecim. Chronic cough in a child. In: EBM Guidelines. Evidence-Based Medicine [Internet]. Helsinki, Finland: Wiley Interscience. John Wiley & Sons; 2007. Available at: http://www.guideline.gov/content.aspx?id=12798. Accessed November 29, 2011.

13. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. Pulm Pharmacol Ther 2009;22(2):159-62. PMID: 19061964.

14. Molassiotis A, Bryan G, Caress A, et al. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. Respir Med 2010;104(7):934-44. PMID: 20385478.

15. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed November 29, 2011.

16. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med 2011;155(8):529-536. PMID: 22007046.

17. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 1998;52(6):377-84. PMID: 9764259.

18. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol 2010;63(5):513-23. PMID: 19595577.

19. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol 2011;64(11):1198-207. PMID: 21463926.

VI. Definition of Terms

ACCP	American College of Chest Physicians
ACE	angiotensin-converting enzyme
BPC	bronchoprovocation challenge
FDA	U.S. Food and Drug Administration
GERD	gastroesophageal reflux disease
HRQOL	health-related quality of life
KQ	key question
NAEB	nonasthmatic eosinophilic bronchitis
NPV	negative predictive value
PPV	positive predictive value
RCT	randomized controlled trial
UACS	upper airway cough syndrome

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
10/04/2012	II. Key Questions	Comparators: KQ 2: All of the above-listed interventions compared both within class and across classes	Comparators: KQ 2: All of the above-listed interventions compared both within class and across classes, as well as with placebo	We have included placebo comparisons due to insufficient data from head-to-head trials to draw conclusions.
10/04/2012	IV. Methods (Comparators)	Inclusion Criteria: KQ 2: All of the above-listed interventions compared both within class and across classes	Inclusion Criteria: KQ 2: All of the above-listed interventions compared both within class and across classes, as well as with placebo	We have included placebo comparisons due to insufficient data from head-to-head trials to draw conclusions.
10/04/2012	IV. Methods (Data Synthesis)		Data Synthesis: We will supplement the meta-analysis of direct comparisons with a mixed treatment meta-analysis that	We have included placebo comparisons and then mixed treatment meta-analysis due to insufficient data from head-to-head trials to draw conclusions.

			incorporates data from placebo comparisons and head-to-head comparisons, including multi-armed trials (i.e., trials that included more than one comparison). The general strategy for analysis will be to construct a random-effects model that is comparable to the standard random-effects models used in the meta-analysis of effect sizes. This model, which will be fitted using SAS® PROC NLMIXED (2009; SAS Institute Inc., Cary, NC), will estimate the effect sizes (relative to placebo) for each treatment	

VIII. Review of Key Questions

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

IX. Key Informants

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

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

X. Technical Experts

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

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

XI. Peer Reviewers

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

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

XII. EPC team disclosures

The EPC team has no conflicts of interest to disclose.

XIII. Role of the Funder

This project was funded under Contract No. 290-07-10066-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements, including the objectivity and independence of the research process and the methodological quality of the report. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

Appendix 1. Medications and Devices

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Nonspecific antitussives (cough suppressants)—anesthetics							
Tessalon	Benzonatate	Teva Pharmaceuticals Inc., USA	All dosages	As needed	Oral	Approved	
Zonatuss	Benzonatate	Atley Pharmaceuticals	All dosages	As needed	Oral	Approved	
Acurate	Codeine	Apotex	All dosages	As needed	Oral	Approved	
Gelonida	Codeine	Pfizer	All dosages	As needed	Oral	Approved	
Tylenol with Codeine Tablets	Codeine	Teva Pharmaceuticals Inc., USA	All dosages	As needed	Oral	Approved	
225+ more brands	Codeine						
Vicodin, Vicodin ES, Vicodin HP	Hydrocodone	Abbott Laboratories	All dosages	As needed	Oral	Approved	
Vicoprofen	Hydrocodone	Teva Pharmaceuticals Inc., USA	All dosages	As needed	Oral	Approved	
Lortab, Tussionex	Hydrocodone	UCB Pharmacy	All dosages	As needed	Oral	Approved	
400+ more brands	Hydrocodone						
Benylin DM	Dextromethorphan	Johnson & Johnson	All dosages	As needed	Oral	Approved	
Robitussin, Dimetapp	Dextromethorphan	Pfizer	All dosages	As needed	Oral	Approved	
NyQuil, Vicks, DayQuil Cough	Dextromethorphan	Procter & Gamble	All dosages	As needed	Oral	Approved	
500+ more brands	Dextromethorphan						

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Protussives—expectorants							
Triaminic, Theraflu	Guaifenesin	Novartis	All dosages	As needed	Oral	Approved	
Dayquil Mucus Control	Guaifenesin	Procter & Gamble	All dosages	As needed	Oral	Approved	
Mucinex	Guaifenesin	Reckitt Benckiser	All dosages	As needed	Oral	Approved	
1000+ more brands	Guaifenesin						
Mucomyst	Acetylcysteine	Bristol-Myers Squibb	All dosages	As needed	Oral	Approved	
Parvolex	Acetylcysteine	GSK	All dosages	As needed	Oral	Approved	
Mucolysin	Acetylcysteine	Sandoz	All dosages	As needed	Oral	Approved	
Protussives—mucolytic or mucus modifying							
Pulmozyme	Dornase alfa inhaled	Genentech	All dosages	As needed	Inhaled (nasal, oral)	Approved	
First-generation antihistamines (H1 blockers)							
Optimine	Azatadine maleate	Schering Corporation	All dosages	As needed	Oral	Approved	
Trexbrom	Brompheniramine	CAPELLON PHARMACEUTICALS	All dosages	As needed	Oral	Approved	
Dicel	Brompheniramine	Centrix Pharmaceutical, Inc.	All dosages	As needed	Oral	Approved	
Dimetapp Allergy Liquigel	Brompheniramine	Pfizer	All dosages	As needed	Oral	Approved	
250+ more brands	Brompheniramine						
Clistin	Carbinoxamine	McNeil Laboratories, Inc	All dosages	As needed	Oral	Approved	
PALGIC	Carbinoxamine	Mikart, Inc. and Pamlab, L.L.C.	All dosages	As needed	Oral	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Vicks Alcohol Free NyQuil (Cold and Cough)	Chlorpheniramine	Procter & Gamble Manufacturing Company	All dosages	As needed	Oral	Approved	
Panadol	Chlorpheniramine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Robitussin Cough and Cold Long-Acting	Chlorpheniramine	Wyeth	All dosages	As needed	Oral	Approved	
700+ more brands	Chlorpheniramine						
Allerhist-1	Clemastine	Cardinal Health	All dosages	As needed	Oral	Approved	
Sunmark 12 Hour Allergy Relief	Clemastine	McKesson	All dosages	As needed	Oral	Approved	
Tavist	Clemastine	Novartis	All dosages	As needed	Oral	Approved	
25+ brands	Cyproheptadine	All generic	All dosages	As needed	Oral		
Dimetapp, Vistaril	Dexchlorpheniramine	Pfizer	All dosages	As needed	Oral	Approved	
Dramamine	Dexchlorpheniramine	Prestige Brands Holdings, Inc.	All dosages	As needed	Oral	Approved	
Polaramin, Trenelone	Dexchlorpheniramine	Schering-Plough	All dosages	As needed	Oral	Approved	
25+ more brands	Dexchlorpheniramine						
Goody's PM Powder, Nytol, Sominex	Diphenhydramine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Benadryl	Diphenhydramine	Pfizer	All dosages	As needed	Oral	Approved	
Therafilm	Diphenhydramine	Novartis	All dosages	As needed	Oral	Approved	
150+ more brands	Diphenhydramine						
Theraflu Nighttime Severe Cold Capsule	Doxylamine	Novartis	All dosages	As needed	Oral	Approved	
Robitussin Night Cold	Doxylamine	Wyeth	All dosages	As needed	Oral	Approved	
Unisom	Doxylamine	Sanofi	All dosages	As needed	Oral	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
100+ more brands	Doxylamine						
Atarax, Vistaril	Hydroxyzine	Pfizer	All dosages	As needed	Oral	Approved	
Atazine	Hydroxyzine	Central Poly Trading	All dosages	As needed	Oral	Approved	
Rezine	Hydroxyzine	Marnel Pharmaceuticals	All dosages	As needed	Oral	Approved	
Patanase	Olopatadine (nasal)	Alcon	All dosages	As needed	Oral	Approved	
Promethegan	Promethazine	Physician's total Care, Inc.	All dosages	As needed	Oral	Approved	
Phenergan	Promethazine	Baxter Healthcare Corporation	All dosages	As needed	Oral	Approved	
200+ more brands	Promethazine						
Zymine	Triprolidine	Vindex Pharmaceuticals	All dosages	As needed	Oral	Approved	
Actidilon, Pro-Actidil	Triprolidine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Myidyl	Triprolidine	USL Pharmaceuticals	All dosages	As needed	Oral	Approved	
40+ more brands	Triprolidine						
Second-generation antihistamines (H1 blockers)							
Benadryl Allergy Relief	Acrivastine	McNeil Laboratories	All dosages	As needed	Oral	Approved	
Semprex-D	Acrivastine	Actient Pharmaceuticals LLC	All dosages	As needed	Oral	Approved	
Astelin	Azelastine (nasal)	MedPointe Healthcare	All dosages	As needed	Oral	Approved	
Astepro	Azelastine (nasal)	Meda Pharmaceuticals Inc.	All dosages	As needed	Oral	Approved	
Aller-Tec	Cetirizine	Ziwell Medical	All dosages	As needed	Oral	Approved	
Analergin	Cetirizine	IVAX	All dosages	As needed	Oral	Approved	
Zyrtec	Cetirizine	McNeil Laboratories	All dosages	As needed	Oral	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Clarinex	Desloratadine	Merck & Co., Inc.	All dosages	As needed	Oral	Approved	
Allegra	Fexofenadine	Sanofi	All dosages	As needed	Oral	Approved	
Wal-Fex	Fexofenadine	Walgreens	All dosages	As needed	Oral	Approved	
Xyzal	Levocetirizine	Sanofi	All dosages	As needed	Oral	Approved	
Claritin	Loratadine	Schering-Plough	All dosages	As needed	Oral	Approved	
Dimetapp ND	Loratadine	Pfizer	All dosages	As needed	Oral	Approved	
Tavist Non-Sedating	Loratadine	Novartis	All dosages	As needed	Oral	Approved	
300+ more brands	Loratadine					Approved	
Inhaled (nasal, oral) corticosteroids							
Beconase/ Beclovent	Beclomethasone	GlaxoSmithKline	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Vancenase/ Vanceril	Beclomethasone	Bayer Schering Pharma	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Qvar	Beclomethasone	IVAX LLC	All dosages	As needed	Inhaled (nasal, oral)	Approved	
200+ more brands	Beclomethasone						
Entocort, Pulmicort, Symbicort	Budesonide	AstraZeneca	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Omnaris, Alvesco	Ciclesonide	Sunovion Pharmaceuticals Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
AeroBid	Flunisolide	Roche; Forest Laboratories	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Bronilide	Flunisolide	Sanofi-Aventis; Boehringer Ingelheim	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Nasarel	Flunisolide	Dabur Pharmaceuticals	All dosages	As needed	Inhaled (nasal, oral)	Approved	
40+ more brands	Flunisolide						
Flonase, Flovent, Advair	Fluticasone	GlaxoSmithKline	All dosages	As needed	Inhaled (nasal, oral)	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Nasonex	Mometasone	Merck & Co., Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Asmanex	Mometasone	Schering-Plough Corp.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Dulera	Mometasone	Dulera	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Trianex	Triamcinolone	Upsher-Smith Laboratories, Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
AllerNaze	Triamcinolone	Lupin Pharma	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Triaderm	Triamcinolone	Crown Laboratories	All dosages	As needed	Inhaled (nasal, oral)	Approved	
90+ more brands	Triamcinolone					Approved	
Oral decongestants							
Robitussin Night Time Cough	Phenylephrine	Wyeth	All dosages	As needed	Oral	Approved	
Alka-Seltzer Plus (Cold and Cough)	Phenylephrine	Bayer Corporation Consumer Care Division	All dosages	As needed	Oral	Approved	
Sudafed PE	Phenylephrine	McNEIL-PPC, Inc.	All dosages	As needed	Oral	Approved	
900+ more brands	Phenylephrine						
Rugby (Nasal Decongestant)	Pseudoephedrine	Rugby Laboratories, Inc.	All dosages	As needed	Oral	Approved	
Sun Mark Sinus (12 hour)	Pseudoephedrine	McKesson	All dosages	As needed	Oral	Approved	
Pseudofed	Pseudoephedrine	McNEIL-PPC, Inc.	All dosages	As needed	Oral	Approved	
900+ more brands	Pseudoephedrine						
Topical decongestants							
Afrin	Oxymetazoline	Schering-Plough Corp.	All dosages	As needed	Topical	Approved	
Mucinex Nasal Spray	Oxymetazoline	Reckitt Benckiser Group plc	All dosages	As needed	Topical	Approved	
Sudafed OM	Oxymetazoline	McNEIL-PPC, Inc.	All dosages	As needed	Topical	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
50+ more brands							
Beta agonists							
Proventil, Volmax	Albuterol	Merck & Co., Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Ventolin	Albuterol	GlaxoSmithKline	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Dulera, Foradil	Formoterol	Schering Corp.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Symbicort	Formoterol	AstraZeneca	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Xopenex	Levalbuterol	Sunovion Pharmaceuticals Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Maxair	Pirbuterol	Graceway Pharmaceuticals	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Advair , Serevent	Salmeterol	GlaxoSmithKline	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Mast cell stabilizers							
Nasalcrom	Cromolyn sodium	Prestige Brands Holdings, Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Inhaled (nasal, oral) anticholinergics							
Atrovent, Combivent	Ipratroprium	Boehringer Ingelheim Pharmaceuticals, Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
DuoNeb	Ipratroprium	Forest Pharmaceuticals Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	
Spiriva HandiHaler	Tiotropium	Boehringer Ingelheim Pharmaceuticals, Inc.	All dosages	As needed	Inhaled (nasal, oral)	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Leukotriene modifiers							
Singulair	Montelukast	Merck & Co., Inc.	All dosages	As needed	Oral	Approved	May cause upper respiratory infection, fever, headache, sore throat, cough, stomach pain, diarrhea, earache or ear infection, flu, runny nose, and sinus infection.
Accolate	Zafirlukast	AstraZeneca	All dosages	As needed	Oral	Approved	
Zyflo	Zileuton	Cornerstone Therapeutics Inc.	All dosages	As needed	Oral	Approved	
H2 blockers							
Tagamet	Cimetidine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Mylanta AR	Famotidine	Johnson & Johnson and Merck	All dosages	As needed	Oral	Approved	
Pepcid	Famotidine	Johnson & Johnson and Merck	All dosages	As needed	Oral	Approved	
Tums Dual Action	Famotidine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Axid, Tazac	Nizatidine	Eli Lilly	All dosages	As needed	Oral	Approved	
Rx-Act Heartburn Relief	Ranitidine	Rx-Act	All dosages	As needed	Oral	Approved	
Zantac	Ranitidine	Boehringer Ingelheim Pharmaceuticals, Inc.	All dosages	As needed	Oral	Approved	
Wal-Zan	Ranitidine	Walgreens	All dosages	As needed	Oral	Approved	
Proton pump inhibitors							
Dexilant	Dexlansoprazole	Takeda Pharmaceuticals America, Inc.	All dosages	As needed	Oral	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Nexium	Esomeprazole	AstraZeneca	All dosages	As needed	Oral	Approved	
Mylanta AR	Famotidine	Johnson & Johnson and Merck	All dosages	As needed	Oral	Approved	
Pepcid	Famotidine	Johnson & Johnson and Merck	All dosages	As needed	Oral	Approved	
Tums Dual Action	Famotidine	GlaxoSmithKline	All dosages	As needed	Oral	Approved	
Prevacid	Lansoprazole	Novartis	All dosages	As needed	Oral	Approved	
Losec	Omeprazole	AstraZeneca	All dosages	As needed	Oral	Approved	
Prilosec	Omeprazole	Procter & Gamble	All dosages	As needed	Oral	Approved	
Zegerid	Omeprazole	Schering-Plough & Santarus	All dosages	As needed	Oral	Approved	
Protonix	Pantoprazole	Wyeth	All dosages	As needed	Oral	Approved	
Nonpharmacologic—physical							
Flutter	Airway oscillating devices	Scandipharm	n/a	As directed	n/a	Approved	
Acapella	Airway oscillating devices	Smiths Medical and DHD Healthcare, Inc.	n/a	As directed	n/a	Approved	
Fluid Flo/Electro Flo	Mechanical percussors	MedSystems	n/a	As directed	n/a	Approved	
Frequencer	Mechanical percussors	Dymedso	n/a	As directed	n/a	Approved	
Resistex PEP Mask	Positive expiratory pressure (PEP) mask	Mercury Medical	n/a	As directed	n/a	Approved	
TheraPep Valve	Positive expiratory pressure (PEP) mask	DHD Healthcare, Inc.	n/a	As directed	n/a	Approved	
PARI PEP Mask	Positive expiratory pressure (PEP) mask	PARI Respiratory Equipment, Inc.	n/a	As directed	n/a	Approved	

Registered or Trademark Name	Generic Name	Manufacturer	Dosage	Frequency	Methods of Administration	FDA Status	Indications/Warnings
Percussionaire	Intrapulmonary percussive ventilator (IPV)	Percussionaire Corporation	n/a	As directed	n/a	Approved	
MedPulse Respiratory Vest System	High-frequency chest compression systems	Electromed, Inc.	n/a	As directed	n/a	Approved	
Vest Airway Clearance System	High-frequency chest compression systems	Hill-Rom	n/a	As directed	n/a	Approved	
ABI Vest, ThAIRapy Vest, ThAIRapy Bronchial Drainage System	High-frequency chest compression systems	Advanced Respiratory	n/a	As directed	n/a	Approved	
CoughAssist/ Exsufflator/ Cofflator	Mechanical insufflation-exsufflation	J.H. Emerson Co.	n/a	As directed	n/a	Approved	

Appendix 2. Literature Search Strategy (11/04/11)

KQ 1: In adults and adolescents (≥ 14 years of age) and children (< 14 years of age), what is the comparative diagnostic accuracy, therapeutic efficacy, and patient outcome efficacy of instruments used to assess cough?

Set #	Terms	Results
#1	cough[MeSH] OR cough[tiab]	29935
#2	cough/diagnosis[mesh] OR pain measurement[mesh] OR severity of illness index[mesh] OR questionnaires[mesh] OR rate[tiab] OR rating[tiab] OR rates[tiab] OR rated[tiab] OR assess*[tiab] OR evaluat*[tiab] OR scale[tiab] OR scales[tiab] monitor*[tiab] OR frequency[tiab] OR frequent[tiab] OR score[tiab] OR scores[tiab] OR "visual analog"[tiab] OR "visual analogue"[tiab]OR severity[tiab] OR sound[tiab] OR sounds[tiab] OR register*[tiab] OR measure*[tiab] OR count*[tiab] OR questionnaire[tiab] OR questionnaires[tiab] **OR instrument[tiab] OR instruments[tiab]**OR (tussigenic[tiab] AND challenge[tiab]) OR "exhaled nitric oxide"[tiab] OR tools[tiab] OR tool[tiab] OR lcq[tiab] OR cqlq[tiab] OR lcm[tiab] OR lifeshirt[tiab] OR lr102[tiab] OR lr100[tiab]	3518335
#3	#1 AND #2	9355
#4	#3 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mesh] NOT humans[mesh])	8196
#5	Limit English	6991

KQ 2: In adults and adolescents (≥ 14 years of age) and children (< 14 years of age), what are the comparative safety and effectiveness of nonspecific (or symptomatic) therapies to treat patients with chronic cough?

a. **In patients with unexplained chronic cough**
b. **In patients with refractory cough with a known underlying etiology**

Set #	Terms	Results
#2	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "prospective"[tw] OR prospectively[tw] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4168822
#5	Cough[mesh] OR cough[ti]	13390
#6	#5 AND #2	4113
	#5 AND #2, Limit to English	3393