APPENDIXES

Appendix A. Exact Search Strings

PubMed® search strategy (November 14, 2011)

KQ 1: Instruments used to assess cough

Set #	Terms
#1	cough[MeSH] OR cough[tiab]
#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]
#3	#1 AND #2
#4	#3 NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mesh] NOT humans[mesh])
#5	#4, Limit English

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	(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])
#2	Cough[mesh] OR cough[ti]
#3	#1 AND #2
#4	#3, Limit to English

Embase® search strategy (November 28, 2011)

Platform: Embase.com

KQ 1: Instruments used to assess cough

Set #	Terms
#1	coughing'/de OR cough:ti OR cough:ab
#2	'coughing'/dm_di OR 'pain assessment'/exp OR 'questionnaire'/exp OR 'instrument'/exp OR "severity of illness":ti OR "severity of illness":ab OR rate:ti OR rate:ab OR rating:ti OR rating:ab OR rates:ti OR rates:ab OR rated:ti OR rated:ab OR assess*:ti OR assess*:ab OR evaluat*:ti OR evaluat*:ab OR scale:ti OR scale:ab OR scales:ti OR scales:ab OR monitor*:ti OR monitor*:ab OR frequency:ti OR frequency:ab OR frequent:ti OR frequent:ab OR score:ti OR score:ab OR scores:ti OR scores:ab OR "visual analog":ti OR "visual analog":ab OR "visual analogue":ti OR "visual analogue":ab OR severity:ti OR severity:ab OR sound:ti OR sound:ab OR sounds:ti OR sounds:ab OR register*:ti OR register*:ab OR measure*:ti OR measure*:ab OR count*:ti OR count*:ab OR questionnaire:ti OR questionnaire:ab OR questionnaires:ti OR questionnaires:ab OR instrument:ti OR instrument:ab OR instruments:ti OR instruments:ab OR (tussigenic:ti AND challenge:ti) OR (tussigenic:ab AND challenge:ab) OR "exhaled nitric oxide":ti OR "exhaled nitric oxide":ab OR tools:ti OR tools:ab OR tool:ti OR tool:ab OR lcq:ti OR lcq:ab OR cqlq:ti OR cqlq:ab OR lcm:ti OR lcm:ab OR lifeshirt:ti OR lifeshirt:ab OR lr102:ti OR lr102:ab OR lr100:ti OR lr100:ab
#3	#1 AND #2
#4	#3 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#4 AND ([embase]/lim NOT [medline]/lim)
#6	#5, Limits: Human, English

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	'coughing'/de OR cough:ti
#2	'randomized controlled trial'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random* OR factorial* OR crossover* OR cross NEAR/1 over* OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer* OR 'clinical study'/exp OR “clinical trial”:ti OR “clinical trial”:ab OR “clinical trials”:ti OR “clinical trials”:ab OR 'evaluation'/exp OR “evaluation study”:ti OR “evaluation study”:ti OR “evaluation studies”:ti OR “evaluation studies”:ab OR “intervention study”:ti OR “intervention study”:ab OR “intervention studies”:ti OR “intervention studies”:ab OR “case control”:ti OR “case control”:ab OR 'cohort analysis'/exp OR cohort:ti OR cohort:ab OR longitudinal*:ti OR longitudinal*:ab OR prospective:ti OR prospective:ab OR prospectively:ti OR prospectively:ab OR retrospective:ti OR retrospective:ab OR 'follow up'/exp OR “follow up”:ti OR “follow up”:ab OR 'comparative effectiveness'/exp OR 'comparative study'/exp OR “comparative study”:ti OR “comparative study”:ab OR “comparative studies”:ti OR “comparative studies”:ab OR 'evidence based medicine'/exp OR “systematic review”:ti OR “systematic review”:ab OR “meta-analysis”:ti OR “meta-analysis”:ab OR “meta-analyses”:ti OR “meta-analyses”:ab
#3	#1 AND #2
#4	#3 NOT ('case report'/exp OR 'case study'/exp OR 'editorial'/exp OR 'letter'/exp OR 'note'/exp)
#5	#4 AND [embase]/lim NOT [medline]/lim
#6	#5, Limits: Human, English

Cochrane search strategy (November 28, 2011)

Platform: Wiley
Database searched: Cochrane Database of Systematic Reviews

KQ 1: Instruments used to assess cough

Set #	Terms
#1	MeSH descriptor Cough explode all trees OR cough:ti,ab
#2	MeSH descriptor Cough explode all trees with qualifier: DI OR MeSH descriptor Pain Measurement explode all trees OR MeSH descriptor Severity of Illness Index explode all trees OR MeSH descriptor Questionnaires explode all trees OR rate:ti,ab OR rating:ti,ab OR rates:ti,ab OR rated:ti,ab OR assess*:ti,ab OR evaluat*:ti,ab OR scale:ti,ab OR scales:ti,ab OR monitor*:ti,ab OR frequency:ti,ab OR frequent:ti,ab OR score:ti,ab OR scores:ti,ab OR “visual analog”:ti,ab OR “visual analogue”:ti,ab OR severity:ti,ab OR sound:ti,ab OR sounds:ti,ab OR register*:ti,ab OR measure*:ti,ab OR count*:ti,ab OR questionnaire:ti,ab OR questionnaires:ti,ab OR instrument:ti,ab OR instruments:ti,ab OR (tussigenic:ti,ab AND challenge:ti,ab) OR "exhaled nitric oxide":ti,ab OR tools:ti,ab OR tool:ti,ab OR lcq:ti,ab OR cqlq:ti,ab OR lcm:ti,ab OR lifeshirt:ti,ab OR lr102:ti,ab OR lr100:ti,ab
#3	#1 AND #2
#4	#3 in Clinical Trials, Systematic Reviews

KQ 2: Nonspecific therapies for chronic cough

Set #	Terms
#1	MeSH descriptor Cough explode all trees OR cough:ti
#2	Limit #1 to Clinical Trials, Systematic Reviews

Grey Literature Searches

ClinicalTrials.gov (February 14, 2012)

Terms: Cough (as condition)

WHO: International Clinical Trials Registry Platform Search Portal (February 14, 2012)

Terms: Cough (in title)

ProQuest COS Conference Papers Index (January 18, 2012)

Set #	Terms
#1	cough[su] OR cough[all]
#2	Limit to 2010-

Appendix B. Data Abstraction Elements

I. Study Characteristics

- Study Dates
- Study Sites
- Geographical Location (Select all that apply)
- Funding Source (Select all that apply)
- Setting (Select all that apply)
- Enrollment Approach (Select all that apply)
    - Consecutive patients
    - Convenience sample (not explicitly consecutive)
    - Not reported/unclear
    - Other – Describe
- Inclusion Criteria: Copy/paste inclusion criteria as reported in the article.
- Exclusion Criteria: Copy/paste exclusion criteria as reported in the article.
- Applicability of Key Questions (Indicate whether the article is applicable to each key question below.)
    - Which populations are included in this study? (Select all that apply)
        - Adults and adolescents (≥14 yrs) with cough
        - Children (<14 years of age) with cough
        - Adults and adolescents (≥14 yrs) with chronic cough
        - Children (<14 years of age) with chronic cough
    - Underlying etiology of cough symptoms in the study population:
        - If Unexplained/idiopathic (Select all that apply)
            - Absence of signs of symptoms of an etiology (NEG S/SX) – Describe
            - Negative diagnostic evaluation (NEG DX) – Describe diagnostic evaluation
            - Lack of response to trial of empiric therapy (NEG EMP TX) – Describe empiric therapy trial and response
            - Other – Describe
        - If Unresponsive/Refractory/Intractable: (Select all that apply)
            - If Known/suspected etiology (Select an answer)
                - Chronic obstructive pulmonary disease (COPD)
                - GERD
                - Asthma
                - Cough-variant asthma
                - UACS (postnasal drip, allergic rhinitis)
                - Interstitial lung disease (sarcoid, etc.)
                - Chronic bronchitis
                - Bronchiectasis, Cystic Fibrosis
                - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc.)
                - Unexplained
                - Other – Describe

            - Positive signs/symptoms – Describe
            - Positive diagnostic evaluation – Describe
            - Other – Describe
            - Specific therapy trial(s) and response – Describe
    - Chronicity – Describe minimum duration required (in weeks)
    - Key Question 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? (Yes/No, This is not a KQ1 article)
    - Key Question 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?
        - In patients with unexplained chronic cough
        - In patients with refractory cough with a known underlying etiology (Yes/No, This is not a KQ2 article)
- Study Enrollment/Study Completion
    - Assessed for eligibility (N)
    - Eligible (N)
    - Randomized (N)
    - Completed follow-up (N)
    - Included in primary outcome analysis (N)
- Comments

II. KQ 1 Instruments

- Author
- Year
- Total N
- Was there a longitudinal component to this study (Yes/No)
- Patient Population – Describe
- Instruments – Include each instrument only once, either under Index or Reference Tests.
    - Index Test/Instrument being evaluated
        - Cough count (by a human)
        - Electronic cough recorder (Sound or pressure)
        - Video cough recorder
        - Tussigenic challenge
        - Cough diaries
        - Score
        - VAS
        - Global Rating Scale
        - If Questionnaire(s) – Questionnaire(s) Name
            - Leicester Cough Questionnaire
            - Cough-specific QoL
            - Chronic Bronchitis Symptoms Assessment Scale
            - Chronic Cough Impact Questionnaire
            - Lung Cancer Cough Questionnaire

            - Cough & Sputum Assessment
            - (A predictive questionnaire)
            - Punum Ladders
            - Adverse Cough Outcome Survey
            - Pediatric Cough Questionnaire
            - Hull Airway Reflux Questionnaire
            - Parent Prox QoL Questionnaire (PC-QoL)
            - Disabkids Questionnaire subscale
            - Cough Severity Diary
        - Other – Describe
    - Reference Test/Comparator
        - Cough count (by a human)
        - Electronic cough recorder (Sound or pressure)
        - Video cough recorder
        - Tussigenic challenge
        - Cough diaries
        - Score
        - VAS
        - Global Rating Scale
        - If Questionnaire(s) – Questionnaire(s) Name
            - Leicester Cough Questionnaire
            - Cough-specific QoL
            - Chronic Bronchitis Symptoms Assessment Scale
            - Chronic Cough Impact Questionnaire
            - Lung Cancer Cough Questionnaire
            - Cough & Sputum Assessment
            - (A predictive questionnaire)
            - Punum Ladders
            - Adverse Cough Outcome Survey
            - Pediatric Cough Questionnaire
            - Hull Airway Reflux Questionnaire
            - Parent Prox QoL Questionnaire (PC-QoL)
            - Disabkids Questionnaire subscale
            - Cough Severity Diary
        - Other – Describe
- Results – Specify what is being compared along with results
- Comments

III. KQ 1 Quality Assessment

- QUADAS-2 Tool for Quality Assessment of Studies of Diagnostic Accuracy
- Rate each risk of bias item listed below as “Yes,” “No,” or “Unclear.” “Yes” indicates low risk of bias, and “No” indicates high risk of bias. After considering each of the quality items, give the study an overall rating of “High risk of bias,” “Low risk of bias,” or “Unclear.” Detailed instructions for each item are provided below. A user's guide

explaining each question and how to score your responses is available in the QUADAS-2 article here: http://www.bris.ac.uk/quadas/quadas-2/

  - Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)
  - Describe the index test and how it was conducted and interpreted
  - Describe the reference standard and how it was conducted and interpreted
  - Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard
  - Was a consecutive or random sample of patients enrolled?
  - Were the index test results interpreted without knowledge of the results of the reference standard?
  - Is the reference standard likely to correctly classify the target condition?
  - Was there an appropriate interval between index test(s) and reference standard?
  - Was a case-control design avoided?
  - If a threshold was used, was it pre-specified?
  - Were the reference standard results interpreted without knowledge of the results of the index test?
  - Did all patients receive a reference standard?
  - Did the study avoid inappropriate exclusions?
  - Did all patients receive the same reference standard?
  - Were all patients included in the analysis?
  - Could the selection of patients have introduced bias?
  - Could the conduct or interpretation of the index test have introduced bias?
  - Could the reference standard, its conduct, or its interpretation have introduced bias?
  - Could the patient flow have introduced bias?
  - Are there concerns that the included patients do not match the review question?
  - Are there concerns that the index test, its conduct, or interpretation differ from the review question?
  - Are there concerns that the target condition as defined by the reference standard does not match the review question?
- Overall study rating
  - Risk of bias is judged as “low”, “high”, or “unclear”. If the answers to all questions in a domain are “yes”, then risk of bias can be judged low. If any question is answered “no”, potential bias exists and previously determined guidelines must be used to make a judgment. The “unclear” category should only be used when insufficient data are reported to permit a judgment.
- Comments

IV. KQ 1 Applicability Assessment

- Population (P)
  - Study population poorly described
  - Inadequate diagnostic evaluation of cough
- Intervention (I)

    - Instrument not well described
    - Highly selected instrument or level of training/proficiency not widely available
    - Doses not reflected in current practice
    - Monitoring practices/visit frequency not in typical practice (e.g., frequent contact, incentives)
    - Older versions of an intervention no longer in common use
    - Cointerventions likely to modify effectiveness of treatment
- Comparator (C)
    - Inadequate comparison therapy
    - Comparator(s) not well described
    - Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
- Outcomes (O)
    - Composite outcomes that mix outcomes of different significance
    - Uses lab assessment such as tussigenic challenge as main outcome
    - Short-term or surrogate outcomes
- Setting (S)
    - Conducted outside of the US and practices not well described or widely divergent relative to US practices
    - Not widely accessible technology
- Comments

V. KQ 2 All Study Arms

- Study type
    - RCT
    - Cohort
    - Crossover
- Common Co-interventions – List common co-interventions across all arms
- Placebo or Control – Treatment Type
    - Placebo
    - No treatment control
    - If Usual care control
        - Is the planned usual care identical for the intervention arm(s) and the comparator arm?
    - Other – Describe
    - Not applicable
- Active Treatment Arm 1 – Treatment Type
    - Pharmacologic Antitussive
        - Anesthetics (e.g., benzonatate)
        - Opiates (e.g., codeine, hydrocodone)
        - Other (e.g., Dextromethorphan) – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Antitussive

        - Foods (e.g., honey, tea, lemon, liquor)
        - Psychological (e.g., cognitive behavioral therapy)
        - Alternative (e.g., acupuncture, tai chi, yoga, meditation)
        - Multidimensional (e.g., speech therapy)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Pharmacologic Protussive
        - Expectorants (e.g., guaifenesin)
        - Mucolytic or mucus modifying (e.g., acetylcysteine, dornase alfa inhaled)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Protussive
        - Physical
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Not applicable
- Active Treatment Arm 2 – Treatment Type
    - Pharmacologic Antitussive
        - Anesthetics (e.g., benzonatate)
        - Opiates (e.g., codeine, hydrocodone)
        - Other (e.g., Dextromethorphan) – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Antitussive
        - Foods (e.g., honey, tea, lemon, liquor)
        - Psychological (e.g., cognitive behavioral therapy)
        - Alternative (e.g., acupuncture, tai chi, yoga, meditation)
        - Multidimensional (e.g., speech therapy)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Pharmacologic Protussive
        - Expectorants (e.g., guaifenesin)

        - Mucolytic or mucus modifying (e.g., acetylcysteine, dornase alfa inhaled)
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Nonpharmacologic Protussive
        - Physical
        - Other – Describe
        - Specific medication or treatment names
        - Frequency (times per day)
        - Duration
        - Dosage
    - Not applicable
- Comments

VI. KQ 2 Baseline Characteristics

- Number of Subjects
    - Total
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs
            - Adults 18+
            - Adults ≥ 65 yrs
            - Other age category – Specify age category used
    - Active Treatment Arm 1 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs

            - Adults 18+
            - Adults ≥ 65 yrs
            - Other age category – Specify age category used
    - Active Treatment Arm 2 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs
            - Adults 18+
            - Adults ≥ 65 yrs
            - Other age category – Specify age category used
    - Placebo or Control – Choose one (Placebo/No treatment control/Usual treatment control/Other)
        - Gender N
            - Total
            - Female
            - Male
        - Age N
            - Infants <6 mo
            - Children 6mo - 2yrs
            - Children 3-6 yrs
            - Children 7-13 yrs
            - Adults/Adolescents 14-64 yrs
            - Adults 18+
            - Adults ≥ 65 yrs
            - Other age category – Specify age category used
- Total Population
    - Age in Years
        - Total
            - Mean
            - Variability – Fill in which type
            - Median
            - Min
            - Max
        - Active Treatment Arm 1 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)

            - Mean
            - Variability – Fill in which type
            - Median
            - Min
            - Max
        - Active Treatment Arm 2 – Choose one (Pharmacologic antitussives/Nonpharmacologic antitussives/Pharmacologic protussives/Nonpharmacologic protussives)
            - Mean
            - Variability – Fill in which type
            - Median
            - Min
            - Max
        - Placebo or Control – Choose one (Placebo/No treatment control/Usual treatment control/Other)
            - Mean
            - Variability – Fill in which type
            - Median
            - Min
            - Max
    - Ethnicity
        - Total
            - Hispanic or Latino
            - Not Hispanic or Latino
        - Treatment Arm 1
            - Hispanic or Latino
            - Not Hispanic or Latino
        - Treatment Arm 2
            - Hispanic or Latino
            - Not Hispanic or Latino
        - Placebo or Control
            - Hispanic or Latino
            - Not Hispanic or Latino
    - Race
        - Total
            - Black/African American
            - American Indian or Alaska Native
            - Asian
            - Native Hawaiian or other Pacific Islander
            - White
            - Multiracial
            - Other – Describe
        - Treatment Arm 1
            - Black/African American

            - American Indian or Alaska Native
            - Asian
            - Native Hawaiian or other Pacific Islander
            - White
            - Multiracial
            - Other – Describe
        - Treatment Arm 2
            - Black/African American
            - American Indian or Alaska Native
            - Asian
            - Native Hawaiian or other Pacific Islander
            - White
            - Multiracial
            - Other – Describe
        - Placebo or Control
            - Black/African American
            - American Indian or Alaska Native
            - Asian
            - Native Hawaiian or other Pacific Islander
            - White
            - Multiracial
            - Other – Describe
- Baseline Characteristics
    - Baseline Characteristics
        - Total
            - Cough severity measure #1 – Describe
                - Mean
                - Median
                - SD
            - Cough severity measure #2 – Describe
                - Mean
                - Median
                - SD
            - Cough severity measure #3 – Describe
                - Mean
                - Median
                - SD
            - Cough frequency – Describe
                - Mean
                - Median
                - SD
            - Cough duration – Describe
                - Mean
                - Median
                - SD

- FEV1 – Describe
    - Mean
    - Median
    - SD
- Tussigenic Challenge #1 – Describe
    - Mean
    - Median
    - SD
- Tussigenic Challenge #2 – Describe
    - Mean
    - Median
    - SD
- Bronchoprovocation challenge – Describe
    - Mean
    - Median
    - SD

- Treatment Arm 1
    - Cough severity measure #1 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe

        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Treatment Arm 2
    - Cough severity measure #1 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe
        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Placebo or Control
    - Cough severity measure #1 – Describe

        - Mean
        - Median
        - SD
    - Cough severity measure #2 – Describe
        - Mean
        - Median
        - SD
    - Cough severity measure #3 – Describe
        - Mean
        - Median
        - SD
    - Cough frequency – Describe
        - Mean
        - Median
        - SD
    - Cough duration – Describe
        - Mean
        - Median
        - SD
    - FEV1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #1 – Describe
        - Mean
        - Median
        - SD
    - Tussigenic Challenge #2 – Describe
        - Mean
        - Median
        - SD
    - Bronchoprovocation challenge – Describe
        - Mean
        - Median
        - SD
- Patient Group Imbalance (Yes/No/Unclear)
- Causes of Chronic Cough
    - Unexplained – If so, describe and provide numbers in table below
    - Known etiology
        - Total
            - Chronic obstructive pulmonary disease (COPD)
                - N
                - %
            - GERD
                - N
                - %

    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N
        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %
    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Treatment Arm 1
    - Chronic obstructive pulmonary disease (COPD)
        - N
        - %
    - GERD
        - N
        - %
    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N

        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %
    - Unexplained
        - N
        - %
    - Other – Describe
        - N
        - %
- Treatment Arm 2
    - Chronic obstructive pulmonary disease (COPD)
        - N
        - %
    - GERD
        - N
        - %
    - Asthma
        - N
        - %
    - Cough-variant asthma
        - N
        - %
    - UACS (postnasal drip, allergic rhinitis)
        - N
        - %
    - Interstitial lung disease (sarcoid, etc.)
        - N
        - %
    - Chronic bronchitis
        - N
        - %
    - Bronchiectasis, Cystic Fibrosis
        - N
        - %
    - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
        - N
        - %

        - Unexplained
            - N
            - %
        - Other – Describe
            - N
            - %
    - Placebo or Control
        - Chronic obstructive pulmonary disease (COPD)
            - N
            - %
        - GERD
            - N
            - %
        - Asthma
            - N
            - %
        - Cough-variant asthma
            - N
            - %
        - UACS (postnasal drip, allergic rhinitis)
            - N
            - %
        - Interstitial lung disease (sarcoid, etc.)
            - N
            - %
        - Chronic bronchitis
            - N
            - %
        - Bronchiectasis, Cystic Fibrosis
            - N
            - %
        - Neuromuscular disease (Duchenne muscular dystrophy, ACS, SCI, etc)
            - N
            - %
        - Unexplained
            - N
            - %
        - Other – Describe
            - N
            - %
- Comments

VII. KQ 2 Quality Assessment

- Study Type
  - If RCT
    - Was the assignment randomized? (Yes/No/Unclear)
    - Was the allocation to study groups, (and interventions) adequately concealed? (Yes/No/Unclear)
  - If Cohort
    - Any attempt to balance the allocation between the groups? (Yes/No/Unclear)
    - Were the criteria applied equally to all groups? (Yes/No/Unclear)
    - Was the selection of the comparison group appropriate? (Yes/No/Unclear)
    - Does the design or analysis control account for important confounding and modifying variables? (Yes/No/Unclear)
    - In cohort studies, is the length of follow-up the same between the groups? (Yes/No/Unclear)
    - Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Other – Describe
- All study types
  - Are baseline characteristics similar between groups? If not, did the analysis control for differences? (Yes/No/Unclear)
  - Did the strategy for recruiting participants into the study differ across study groups? (Yes/No/Unclear)
  - Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results? (Yes/No/Unclear)
  - Did variation from the study protocol compromise the conclusions of the study?
  - Was there a high rate of differential or overall attrition? (Yes/No/Unclear)
  - Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up? (Yes/No/Unclear)
  - Is the analysis conducted on an intention-to-treat (ITT) basis? (Yes/No/Unclear)
  - Were the outcome assessors blinded to the intervention or exposure status of participants? (Yes/No/Unclear)
  - Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants? (Yes/No/Unclear)
  - Were incomplete/missing outcome data adequately reported and the data managed by an accepted method? (Yes/No/Unclear)
  - Was the primary outcome pre-specified? Are all pre-specified outcomes reported? (Yes/No/Unclear)
  - Was there a substantive conflict of interest which posed a substantive, important threat to validity of the results? (Yes/No/Unclear)
- Overall study rating

- Please assign each study an overall quality rating of “Good,” “Fair,” or “Poor” based on the following definitions. “Fair” is the initial assumption for cohort studies, unless there is significant evidence to prove that it could be categorized as “Good”.
- Quality Rating
    - Good
    - Fair
    - Poor
        - If “Fair” or “Poor,” provide rationale for decision.

VIII. KQ 2 Applicability Assessment

- Population (P)
    - Study population poorly described
    - Inadequate diagnostic evaluation of cough
- Intervention (I)
    - Intervention not well described
    - Highly selected intervention team or level of training/proficiency not widely available
    - Doses not reflected in current practice
    - Monitoring practices/visit frequency not in typical practice (e.g., frequent contact, incentives)
    - Older versions of an intervention no longer in common use
    - Cointerventions likely to modify effectiveness of treatment
- Comparator (C)
    - Inadequate comparison therapy
    - Comparator(s) not well described
    - Use of substandard alternative therapy (e.g., standard of treatment not from current practice)
- Outcomes (O)
    - Composite outcomes that mix outcomes of different significance
    - Uses lab assessment such as tussigenic challenge as main outcome
    - Short-term or surrogate outcomes
- Setting (S)
    - Conducted outside of the US and practices not well described or widely divergent relative to US practices
    - Not widely accessible technology
- Comments

Appendix C. List of Included Studies

Aliprandi P, Castelli C, Bernorio S, et al. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41. PMID: 15553659.

Archer LN, Simpson H. Night cough counts and diary card scores in asthma. Arch Dis Child. 1985;60(5):473-4. PMID: 4015154.

Au DH, Blough DK, Kirchdoerfer L, et al. Development of a quantifiable symptom assessment tool for patients with chronic bronchitis: the Chronic Bronchitis Symptoms Assessment Scale. COPD. 2005;2(2):209-16. PMID: 17136947.

Aversa C, Cazzola M, Clini V, et al. Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases. Drugs Exp Clin Res. 1993;19(6):273-9. PMID: 8013271.

Baiardini I, Braido F, Fassio O, et al. A new tool to assess and monitor the burden of chronic cough on quality of life: Chronic Cough Impact Questionnaire. Allergy. 2005;60(4):482-8. PMID: 15727580.

Barnabe R, Berni F, Clini V, et al. The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough. Monaldi Arch Chest Dis. 1995;50(2):93-7. PMID: 7613554.

Barry SJ, Dane AD, Morice AH, et al. The automatic recognition and counting of cough. Cough. 2006;2:8. PMID: 17007636.

Birring SS, Fleming T, Matos S, et al. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. Eur Respir J. 2008;31(5):1013-8. PMID: 18184683.

Birring SS, Matos S, Patel RB, et al. Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med. 2006;100(6):1105-9. PMID: 16266801.

Birring SS, Prudon B, Carr AJ, et al. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-43. PMID: 12668799.

Braido F, Baiardini I, Tarantini F, et al. Chronic cough and QoL in allergic and respiratory diseases measured by a new specific validated tool-CCIQ. J Investig Allergol Clin Immunol. 2006;16(2):110-6. PMID: 16689184.

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Chang AB, Newman RG, Carlin JB, et al. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. Eur Respir J. 1998;11(2):462-6. PMID: 9551755.

Chang AB, Newman RG, Phelan PD, et al. A new use for an old Holter monitor: an ambulatory cough meter. Eur Respir J. 1997;10(7):1637-9. PMID: 9230259.

Chang AB, Phelan PD, Robertson CF, et al. Relation between measurements of cough severity. Arch Dis Child. 2003;88(1):57-60. PMID: 12495964.

Chernecky C, Sarna L, Waller JL, et al. Assessing coughing and wheezing in lung cancer: a pilot study. Oncol Nurs Forum. 2004;31(6):1095-101. PMID: 15547632.

Clarke SW, Lopez-Vidriero MT, Pavia D, et al. The effect of sodium 2-mercapto-ethane sulphonate and hypertonic saline aerosols on bronchial clearance in chronic bronchitis. Br J Clin Pharmacol. 1979;7(1):39-44. PMID: 104724.

Corrigan DL, Paton JY. Pilot study of objective cough monitoring in infants. Pediatr Pulmonol. 2003;35(5):350-7. PMID: 12687591.

Coyle MA, Keenan DB, Henderson LS, et al. Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough. 2005;1:3. PMID: 16270923.

Crawford B, Monz B, Hohlfeld J, et al. Development and validation of a cough and sputum assessment questionnaire. Respir Med. 2008;102(11):1545-55. PMID: 18662868.

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during ambulatory monitoring? Thorax. 2007;62(4):329-34. PMID: 17101736.

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Dierckx P, Leblanc G, Decoster A, et al. Double-blind study of glaucine in chronic cough. Int J Clin Pharmacol Ther Toxicol. 1981;19(9):396-9. PMID: 7028646.

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Doherty MJ, Mister R, Pearson MG, et al. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax. 2000;55(8):643-9. PMID: 10899239.

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Falconer A, Oldman C, Helms P. Poor agreement between reported and recorded nocturnal cough in asthma. Pediatr Pulmonol. 1993;15(4):209-11. PMID: 8469572.

Faniran AO, Peat JK, Woolcock AJ. Measuring persistent cough in children in epidemiological studies: development of a questionnaire and assessment of prevalence in two countries. Chest. 1999;115(2):434-9. PMID: 10027444.

Faruqi S, Thompson R, Wright C, et al. Quantifying chronic cough: objective versus subjective measurements. Respirology. 2011;16(2):314-20. PMID: 21054670.

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Fletcher KE, French CT, Irwin RS, et al. A prospective global measure, the Punum Ladder, provides more valid assessments of quality of life than a retrospective transition measure. J Clin Epidemiol. 2010;63(10):1123-31. PMID: 20303709.

Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol. 1997;49(10):1045-9. PMID: 9364418.

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French CT, Irwin RS, Fletcher KE, et al. Evaluation of a cough-specific quality-of-life questionnaire. Chest. 2002;121(4):1123-31. PMID: 11948042.

Gastpar H, Criscuolo D, Dieterich HA. Efficacy and tolerability of glaucine as an antitussive agent. Curr Med Res Opin. 1984;9(1):21-7. PMID: 6373156.

Guyatt GH, Townsend M, Kazim F, et al. A controlled trial of ambroxol in chronic bronchitis. Chest. 1987;92(4):618-20. PMID: 3308343.

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Huisman AN, Wu MZ, Uil SM, et al. Reliability and validity of a Dutch version of the Leicester Cough Questionnaire. Cough. 2007;3:3. PMID: 17313670.

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Jones RM, Hilldrup S, Hope-Gill BD, et al. Mechanical induction of cough in Idiopathic Pulmonary Fibrosis. Cough. 2011;7:2. PMID: 21477349.

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Kelsall A, Decalmer S, Webster D, et al. How to quantify coughing: correlations with quality of life in chronic cough. Eur Respir J. 2008;32(1):175-9. PMID: 18287128.

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Ma W, Yu L, Wang Y, et al. Changes in health-related quality of life and clinical implications in Chinese patients with chronic cough. Cough. 2009;5:7. PMID: 19781068.

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Matos S, Birring SS, Pavord ID, et al. An automated system for 24-h monitoring of cough frequency: the Leicester Cough Monitor. IEEE Trans Biomed Eng. 2007;54(8):1472-9. PMID: 17694868.

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Matts SG. A trial of Lotussin and linctus diphenhydramine in patients wth an irritant cough. J Int Med Res. 1977;5(6):470-2. PMID: 338397.

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Morice AH, Menon MS, Mulrennan SA, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312-5. PMID: 17122382.

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Paul IM, Wai K, Jewell SJ, et al. Evaluation of a new self-contained, ambulatory, objective cough monitor. Cough. 2006;2:7. PMID: 17005042.

Polley L, Yaman N, Heaney L, et al. Impact of cough across different chronic respiratory diseases: comparison of two cough-specific health-related quality of life questionnaires. Chest. 2008;134(2):295-302. PMID: 18071022.

Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? Handb Exp Pharmacol. 2009(187):311-20. PMID: 18825348.

Ramsay J, Wright C, Thompson R, et al. Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. Br J Clin Pharmacol. 2008;65(5):737-41. PMID: 18279476.

Reid JJ. Double-blind trial of ketotifen in childhood chronic cough and wheeze. Immunol Allergy Pract. 1989;11(4):143-50.

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Simon SW. A comparative study of two new non-narcotic antitussive drugs. Ohio Med. 1957;53(12):1426-7. PMID: 13493953.

Simon SW. Symptomatic treatment of asthmatic bronchitis. J Am Geriatr Soc. 1960;8:107-11. PMID: 14446944.

Singapuri A, McKenna S, Brightling CE. The utility of the mannitol challenge in the assessment of chronic cough: a pilot study. Cough. 2008;4:10. PMID: 19017380.

Smith J, Owen E, Earis J, et al. Cough in COPD: correlation of objective monitoring with cough challenge and subjective assessments. Chest. 2006;130(2):379-85. PMID: 16899835.

Smith JA, Earis JE, Woodcock AA. Establishing a gold standard for manual cough counting: video versus digital audio recordings. Cough. 2006;2:6. PMID: 16887019.

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Vertigan AE, Theodoros DG, Gibson PG, et al. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. Thorax. 2006;61(12):1065-9. PMID: 16844725.

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Yousaf N, Monteiro W, Parker D, et al. Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial. Thorax. 2010;65(12):1107-10. PMID: 20965928.

Appendix D. List of Excluded Studies

All studies listed below were reviewed in their full-text version and excluded for the reasons cited. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Full text not available

Li Y, Wang H. 100 Cases of children cough and gasp treated by fire needling. Chinese Journal of Acupuncture and Moxibustion. 1991;4(2):117-118.

Maesen F, Smeets J, Hoogslag MA. Azipranone (RU 20.201), a new cough suppressant. A clinical trial using objective and subjective parameters. Tijdschrift voor Geneesmiddelenonderzoek. 1983;8(7):1941-1944.

Non-English language

Ghodrati S, Mousavinasab SN, Pezeshki B, et al. Prevalence of cough variant asthma in patients with chronic cough attending to Vali-e Asr hospital of Zanjan, Iran, 2009. Journal of Zanjan University of Medical Sciences and Health Services. 2011;19(76).

Kardos P, Gebhardt T. Chronic persistent cough (CPH) in the medical practice: Diagnostics and treatment of 329 patients in 2 years. Pneumologie. 1996;50(6):437-441.

Zhang YM, Lin JT. The values of fractional exhaled nitric oxide for the diagnosis and treatment response evaluation of chronic cough. Respirology. 2011;16:219.

Study population is not human

Chakraborty D, Shah B. Antimicrobial, anti-oxidative and anti-hemolytic activity of Piper betel leaf extracts. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(SUPPL. 3):192-199.

Harsanyi K, Tardos L, Feher I, et al. Pharmacologic, clinico-pharmacologic and clinical effects of Libexin. Boll Chim Farm. 1973;112(10):691-9. PMID: 4782264.

Schneider CR, Everett AW, Geelhoed E, et al. Provision of primary care to patients with chronic cough in the community pharmacy setting. Ann Pharmacother. 2011;45(3):402-8. PMID: 21325099.

Not an evaluation study (KQ 1), RCT (KQ1 or KQ2), cohort study (KQ1 or KQ2), systematic review, or meta-analysis

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Anonymous. Cough medication evaluation. JAMA. 1966;197(7):581-2. PMID: 5952817.

Anonymous. Cough suppressants ineffective for children. Journal of Family Practice. 2004;53(10):770-772.

Anonymous. Prolonged cough and chronic cough. Respirology. 2006;11(Suppl 4):S141-S142.

Anonymous. Prolonged and chronic cough. Respirology. 2006;11(Suppl 4):S160-S174.

Anonymous. Evaluation of cough. Respirology. 2006;11(Suppl 4):S143-S148.

Anonymous. Acute cough. Respirology. 2006;11(Suppl 4):S152-S159.

Anonymous. Cough in specific populations (paediatric patients, elderly patients and patients with underlying disease). Respirology. 2006;11(Suppl 4):S175-S186.

Axelsson I. Honey, not dextromethorphan, was better than no treatment for nocturnal cough in children with upper respiratory infections: Commentary. Evidence-Based Medicine. 2008;13(4):106.

Bailey EJ, Chang AB, Thomas D. In children with prolonged cough, does treatment with antibiotics have a better effect on cough resolution than no treatment? Part A: Evidence-based answer and summary. Paediatrics and Child Health. 2008;13(6):512-513.

Banner AS. Cough: physiology, evaluation, and treatment. Lung. 1986;164(2):79-92. PMID: 3084882.

Barraclough K. Diagnosis in general practice: Chronic cough in adults. BMJ. 2009;338(7705):1267.

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Appendix E. QUADAS-2 Scoring of KQ 1 Studies

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded from the 2x2	Random sample	Index test results	Reference standard correct	Appropriate interval	Case-control design avoided	Threshold pre-specified	Reference standard results	Reference standard all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Index test match review question	Interpretation match review question	Target condition match review question	Study Rating
Archer, 1985[1]	Y	Y	Y	N	U	U	Y	Y	Y	U	U	Y	Y	Y	N	N	N	N	N	N	N	N	High risk of bias
Au, 2005[2]	Y	Y	N	N	N	U	Y	Y	Y	U	U	N	Y	N	N	N	N	N	Y	N	N	N	High risk of bias
Baiardini, 2005[3]	N	Y	Y	Y	U	U	U	U	Y	U	U	U	U	U	Y	Y	N	Y	Y	Y	N	Y	High risk of bias
Barry, 2006[4]	U	Y	U	U	U	Y	Y	U	Y	U	Y	N	U	Y	Y	Y	Y	Y	Y	N	N	N	Low risk of bias
Birring, 2008[5]	Y	Y	Y	U	Y	Y	Y	Y	N	U	Y	N	Y	N	Y	U	U	N	Y	N	N	N	Low risk of bias
Birring, 2006[6]	Y	Y	Y	U	Y	U	Y	U	N	U	U	Y	Y	Y	Y	N	Y	N	Y	N	N	N	Low risk of bias
Birring, 2003[7]	Y	Y	Y	Y	N	U	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	U	N	N	N	N	Low risk of bias
Braido, 2006[8]	Y	Y	Y	U	Y	U	Y	U	N	U	U	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Chang, 1998[9]	Y	Y	Y	U	U	U	U	Y	Y	U	Y	U	Y	Y	N	U	U	N	U	N	N	N	Low risk of bias
Chang, 1997[10]	N	Y	Y	Y	U	U	Y	Y	N	U	U	Y	Y	Y	N	Y	N	N	N	N	N	N	Low risk of bias
Chang, 2003[11]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	U	N	N	N	N	N	N	Low risk of bias
Chernecky, 2004[12]	Y	Y	U	Y	N	U	U	Y	Y	U	U	N	Y	Y	Y	Y	N	Y	Y	N	N	N	High risk of bias
Corrigan, 2003[13]	Y	Y	Y	Y	U	Y	Y	Y	N	U	Y	N	Y	Y	N	U	N	N	Y	N	N	N	Low risk of bias
Coyle, 2005[14]	U	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Crawford, 2008[15]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	N	Y	N	N	N	N	N	N	Low risk of bias
Dales, 1997[16]	N	Y	Y	N	N	Y	Y	Y	Y	U	Y	Y	U	Y	Y	N	N	N	N	Y	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded from the 2x2	Random sample	Index test results	Reference standard correct	Appropriate interval	Case-control design avoided	Threshold pre-specified	Reference standard results	Reference standard all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Index test match review question	Interpretation match review question	Target condition match review question	Study Rating
De Vito Dabbs, 2002[17]	Y	Y	Y	N	Y	Y	Y	Y	Y	U	Y	U	Y	U	U	N	N	N	U	Y	Y	N	Low risk of bias
Decalmer, 2007[18]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Dicpinigaitis, 2006[19]	N	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	Y	U	N	N	N	High risk of bias
Doherty, 2000[20]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	Y	N	N	N	High risk of bias
Falconer, 1993[21]	N	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	U	Y	N	Y	N	N	Y	N	N	N	High risk of bias
Faniran, 1999[22]	Y	Y	U	U	N	Y	U	U	Y	U	U	U	N	U	N	Y	N	U	U	Y	N	U	High risk of bias
Faruqi, 2011[23]	Y	Y	U	U	U	Y	U	U	Y	U	U	U	Y	U	Y	N	N	U	N	N	N	U	Low risk of bias
Fisman, 2001[24]	Y	Y	N	Y	Y	Y	N	N	Y	U	N	N	Y	N	Y	Y	N	N	N	N	N	N	High risk of bias
Fletcher, 2010[25]	Y	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Freestone, 1997[26]	Y	Y	N	N	U	Y	N	N	Y	U	N	N	Y	N	N	Y	N	N	Y	N	N	N	Low risk of bias
French, 1998[27]	Y	Y	Y	N	N	Y	Y	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
French, 2002[28]	Y	Y	N	N	N	Y	N	N	Y	U	N	N	Y	N	Y	N	N	N	N	N	N	N	Low risk of bias
Hamutcu, 2002[29]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	U	Y	U	Y	N	Y	Y	N	N	N	N	Low risk of bias
Hartnick, 2009[30]	Y	Y	U	Y	N	Y	U	Y	Y	U	N	Y	Y	Y	Y	U	U	Y	N	N	N	N	Low risk of bias
Hoskyns, 1991[31]	Y	Y	N	Y	N	Y	U	Y	Y	U	U	Y	Y	Y	Y	U	N	U	N	N	N	N	Low risk of bias
Hsu, 1994[32]	N	Y	N	N	N	Y	U	Y	Y	U	U	U	Y	Y	U	N	N	Y	N	N	N	N	Low risk of bias
Huisman, 2007[33]	U	Y	Y	U	Y	Y	U	Y	Y	U	Y	Y	Y	Y	U	N	N	N	N	N	N	N	Low risk of bias
Jones, 2011[34]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	U	Y	Y	U	N	N	N	N	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded from the 2x2	Random sample	Index test results	Reference standard correct	Appropriate interval	Case-control design avoided	Threshold pre-specified	Reference standard results	Reference standard all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Index test match review question	Interpretation match review question	Target condition match review question	Study Rating
Kalpaklioglu, 2005[35]	U	Y	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Kelsall, 2008[36]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	Y	U	U	U	N	N	N	Low risk of bias
Kelsall, 2011[37]	Y	Y	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	N	Y	N	N	Y	N	N	N	Low risk of bias
Key, 2010[38]	N	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	N	N	N	N	Low risk of bias
Krahnke, 2004[39]	U	Y	Y	N	U	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	N	N	N	N	N	N	Low risk of bias
Krajnik, 2010[40]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	N	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
Ma, 2009[41]	U	Y	Y	N	Y	U	Y	Y	Y	U	U	Y	Y	Y	U	N	N	Y	U	N	N	N	Low risk of bias
Marsden, 2008[42]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	U	Y	Y	U	U	N	U	N	N	N	N	Low risk of bias
Matos, 2007[43]	U	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	N	N	N	N	N	N	N	N	Low risk of bias
Monz, 2010[44]	Y	Y	Y	U	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	U	N	N	N	N	N	N	Low risk of bias
Murray, 2009[45]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	N	Y	N	Y	Low risk of bias
Mwachari, 2007[46]	Y	Y	U	U	U	Y	U	U	Y	U	U	U	Y	U	Y	Y	N	U	N	N	Y	U	Low risk of bias
Nandha, 2000[47]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Low risk of bias
Newcombe, 2011[48]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	U	N	N	N	Low risk of bias
Newcombe, 2008[49]	Y	Y	Y	Y	U	Y	U	Y	Y	U	Y	Y	Y	Y	U	Y	N	U	U	N	N	N	Low risk of bias
Newcombe, 2010[50]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	N	N	U	N	N	N	Low risk of bias
Nieto, 2003[51]	Y	Y	U	U	U	Y	U	U	Y	Y	U	U	Y	U	U	Y	N	U	U	N	N	U	Low risk of bias
O'Connell 1994[52]	Y	Y	Y	Y	Y	Y	U	Y	Y	U	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	Low risk of bias

Study	Methods of patient selection described	Index test described	Reference standard described	Excluded from the 2x2	Random sample	Index test results	Reference standard correct	Appropriate interval	Case-control design avoided	Threshold pre-specified	Reference standard results	Reference standard all patients	Inappropriate exclusions avoided	Same reference standard for all	All patients included in analysis	Selection of patients bias	Index text interpretation bias	Reference standard interpretation bias	Patient flow bias	Index test match review question	Interpretation match review question	Target condition match review question	Study Rating
Paul, 2006[53]	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	U	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Polley, 2008[54]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Raj, 2009[55]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Singapuri, 2008[56]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Smith, 2006[57]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Smith, 2006[58]	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	Y	N	N	N	Low risk of bias
Vernon, 2010[59]	Y	Y	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	N	N	N	N	N	N	N	Low risk of bias
Thomas, 1978[60]	N	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	U	Y	U	Y	N	N	N	N	N	N	Low risk of bias

Abbreviations: N = No; Y = Yes; U = Unclear

References to Appendix E

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