

## ONLINE SUPPLEMENT 1

### **PREVENTION OF COPD EXACERBATIONS: An European Respiratory Society/American Thoracic Society (ERS/ATS) guideline.**

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## **FULL METHODS SECTION**

### **Group composition**

The guideline panel co-chairs (JAW, JAK) were selected by the European Respiratory Society (ERS) and American Thoracic Society (ATS). They led all aspects of project management and selected the panellists, which included 11 clinicians with experience in COPD management and research. In addition, there were two methodologists (TT, DR) and a clinician-methodologist (KCW). The lead methodologist (TT) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met, with assistance from the other methodologists. The co-chairs and panellists discussed the evidence and formulated the recommendations; the methodologists did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest. At least 50% of the co-chairs and 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest took part in the discussions about the evidence but did not participate in the formulation of recommendations.

### **Formulation of questions**

Guideline panel members compiled a list of issues that they considered important and relevant to the treatment of COPD exacerbations. The questions were rephrased by the lead methodologist using the Population, Intervention, Comparator, and Outcomes (PICO) format (1). Discussion and consensus among the co-chairs and panellists was used to identify the ~~six~~ five questions that would be addressed in the guideline.

### **Rating the importance of outcomes**

After choosing the questions, the guideline panel identified outcomes that they considered relevant to each question prior to conducting the literature search. They rated the importance of each outcome using a scale from 1 to 9 (a rating of 1 to 3 was assigned to outcomes of low importance for decision-making, 4 to 6 to outcomes important for decision-making, and 7 to 9 to outcomes critically important for decision-making). A teleconference was convened during which the ratings were discussed and some additional outcomes were rated. At the conclusion of the teleconference, all outcomes were categorized as “critical”, “important”, or “not important” for decision-making. The reason for the distinction is that only critical outcomes are used to determine the overall quality of evidence for a recommendation, even though the quality of evidence is assessed for every outcome as indicated in the research protocols.

**Research protocols (questions, objectives, inclusion criteria, outcomes of interest, search strategy) for prevention of COPD exacerbations**

<b>Research Protocol, Question 1</b>	
<b>Question</b>	Should mucolytics be used for prevention of exacerbations in people with stable COPD?
<b>Objective</b>	To compare mucolytics to placebo for prevention COPD exacerbations in stable patients with COPD
<b>Criteria</b>	SRs and RCTs with minimum 12 month treatment period comparing mucolytics with placebo in adults with stable COPD
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Number of exacerbations (critical)</li> <li>• QoL (critical)</li> <li>• Hospitalisations (critical)</li> <li>• Patients with 0 exacerbations (important)</li> <li>• AEs (important)</li> <li>• Mortality (important)</li> <li>• Decrease of sputum production (important)</li> <li>• FEV1 (not important)</li> <li>• FVC (not important)</li> </ul>
<b>Search strategy</b>	<p>COPD population AND MUCOLYTICS.</p> <p>Sources: Medline, Embase, Cochrane. Limits: Study Types: RCTs, SRs, Years: 2009-2016, Language: English</p>

<b>Research Protocol, Question 2</b>	
<b>Question</b>	Are LAMAs or LABAs more effective in preventing exacerbation in patients with stable COPD?
<b>Objective</b>	To compare LAMAs versus LABAs for prevention of COPD exacerbations
<b>Criteria</b>	SRs and RCTs with minimum 12 month treatment period comparing LAMAs with LABAs in adults with stable COPD
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Exacerbations (critical)</li> <li>• Morality (critical)</li> <li>• Hospitalisation (critical)</li> <li>• AEs (critical)</li> <li>• QoL (critical)</li> </ul>

	<ul style="list-style-type: none"> <li>• FEV1 (critical)</li> <li>• Breathlessness (important)</li> <li>• Exercise tolerance (important)</li> </ul>
<b>Search strategy</b>	<p>COPD population AND LAMAs/LABAs</p> <p>Sources: Medline, Embase, Cochrane. Limits: Study Types: RCTs, SRs, Years: 2009-2016, Language: English</p>

<b>Research Protocol, Question 3</b>	
<b>Question</b>	Should PDEIVs be used for preventing exacerbation in patients with stable COPD and a history of exacerbations/ chronic bronchitis?
<b>Objective</b>	To compare PDEIVs to placebo for preventing COPD exacerbations
<b>Criteria</b>	SRs and RCTs with minimum 12 month treatment period comparing PDEIVs with placebo in adults with stable COPD and a history of exacerbations/ chronic bronchitis
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Patients with at least 1 exacerbation (critical)</li> <li>• AEs (critical)</li> <li>• Mortality (critical)</li> <li>• Rate of exacerbations (critical)</li> <li>• Time to exacerbation (critical)</li> <li>• CV events (critical)</li> <li>• QoL (important)</li> <li>• FEV1 (important)</li> <li>• FVC (important)</li> </ul>
<b>Search strategy</b>	<p>COPD population AND PDEIVs</p> <p>Sources: Medline, Embase, Cochrane. Limits: Study Types: RCTs, SRs, Years: 2003-2016, Language: English</p>

<b>Research Protocol, Question 4</b>	
<b>Question</b>	Should quinolones be used for preventing exacerbations in people with stable COPD?
<b>Objective</b>	To compare quinolones to placebo for preventing exacerbations in patients with stable COPD
<b>Criteria</b>	SRs and RCTs with minimum 12 month treatment period comparing quinolones with placebo in adults with stable COPD and a history of exacerbations

<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Time to first exacerbation (critical)</li> <li>• Exacerbation rates (critical)</li> <li>• Hospitalisation (critical)</li> <li>• AEs (critical)</li> <li>• Mortality (critical)</li> <li>• QoL (important)</li> <li>• Reduction in airway bacterial load (important)</li> <li>• FEV1 (not important)</li> </ul>
<b>Search strategy</b>	<p>COPD population AND ANTIBIOTICS</p> <p>Sources: Medline, Embase, Cochrane. Limits: Study Types: RCTs, SRs, Years: 2003-2016, Language: English</p>

<b>Research Protocol, Question 5</b>	
<b>Question</b>	Should macrolides be used for preventing exacerbations in people with stable COPD?
<b>Objective</b>	To compare macrolides to placebo for preventing exacerbations in patients with stable COPD
<b>Criteria</b>	SRs and RCTs with minimum 12 month treatment period comparing macrolides with placebo in adults with stable COPD and a history of exacerbations
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>• Time to first exacerbation (critical)</li> <li>• Exacerbation rates (critical)</li> <li>• Hospitalisation (critical)</li> <li>• AEs (critical)</li> <li>• Mortality (critical)</li> <li>• QoL (important)</li> <li>• Reduction in airway bacterial load (important)</li> <li>• FEV1 (not important)</li> </ul>
<b>Search strategy</b>	<p>COPD population AND ANTIBIOTICS</p> <p>Sources: Medline, Embase, Cochrane. Limits: Study Types: RCTs, SRs, Years: 2003-2016, Language: English</p>

## Literature searches

Our literature searches used the National Institute of Health and Clinical Excellence (NICE) guidelines as a starting point (2,3). For questions that were addressed in the 2004 NICE guidelines, we conducted literature searches in Medline, Embase, and the Cochrane Database of Systematic Reviews beginning in 2003. For questions that were addressed in the 2010 NICE guidelines, we conducted literature searches in the same databases beginning in 2009. Initial searches were conducted in January 2012 and then updated in June 2012, February 2013, and September 2015. We used the same or similar search strategies as those used by NICE. To search Embase and Medline, we searched only the English speaking literature using the search strategy shown below, whereas to search the Cochrane Database of Systematic Reviews, we used the search term, “chronic obstructive pulmonary disease”.

## Search strategies- COPD population AND Antibiotics

Embase

#9

#8 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2003-2012]/py

#8

#1 AND #7

#7

#2 OR #3 OR #4 OR #6

#6

ciprofloxacin:ab,ti OR gatifloxacin:ab,ti OR gemfloxacin:ab,ti OR grepafloxacin:ab,ti OR levofloxacin:ab,ti OR lomefloxacin:ab,ti OR moxifloxacin:ab,ti OR ofloxacin:ab,ti OR sparfloxacin:ab,ti

#5

azithromycin:ab,ti OR clarithromycin:ab,ti OR dirithromycin:ab,ti OR erithromycin:ab,ti OR roxithromycin:ab,ti OR telithromycin:ab,ti OR troleandomycin:ab,ti

#4

'quinoline derived antiinfective agent'/exp

#3

'quinolone'/exp

#2

'macrolide'/exp

#1

#1.67

#1.42 AND #1.66

#1.66

#1.51 OR #1.65

#1.65

#1.52 OR #1.53 OR #1.54 OR #1.55 OR #1.56 OR #1.57 OR #1.58 OR #1.59 OR #1.60 OR #1.61  
OR #1.62 OR #1.63 OR #1.64

#1.64

((crossover OR 'cross over' OR 'cross over') NEXT/2 (design\* OR stud\* OR procedure\* OR  
trial\*)):ab,ti AND [2003-2012]/py

#1.63

'crossover procedure'/exp AND [2003-2012]/py

#1.62

((singl\* OR double\* OR triple\* OR treble\*) NEXT/5 (blind\* OR mask\*)):ab,ti AND [2003-  
2012]/py

#1.61

random\*:ab,ti AND [2003-2012]/py

#1.60

placebo:ab,ti AND [2003-2012]/py

#1.59

'randomization'/exp AND [2003-2012]/py

#1.58

'clinical article'/exp AND [2003-2012]/py

#1.57

((clinical\* OR control\* OR compar\*) NEXT/3 (trial\* OR study OR studies)):ab,ti AND [2003-  
2012]/py

#1.56

'double blind procedure'/exp AND [2003-2012]/py

#1.55

'placebo'/exp AND [2003-2012]/py

#1.54

'clinical study'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'phase 1 clinical  
trial'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical  
trial'/exp AND [2003-2012]/py

#1.53

'clinical trial'/exp AND [2003-2012]/py

#1.52

'controlled study'/exp OR 'randomized controlled trial'/exp AND [2003-2012]/py

#1.51

#1.45 OR #1.46 OR #1.47 OR #1.48 OR #1.49 OR #1.50

#1.50

((pool\* OR combined OR combining) NEXT/1 (data OR trials OR studies OR results)):ab,ti AND [2003-2012]/py

#1.49

((systematic\* OR evidence\* OR methodol\* OR quantitativ\*) NEXT/5 (review\* OR survey\* OR overview\*)):ab,ti AND [2003-2012]/py

#1.48

'meta-analysis':ab,ti OR metanaly\*:ab,ti OR metaanaly\*:ab,ti OR 'meta analysis':ab,ti AND [2003-2012]/py

#1.47

'systematic review'/exp AND [2003-2012]/py

#1.46

'meta analysis'/exp AND [2003-2012]/py

#1.45

#1.43 AND #1.44

#1.44

systematic:ab,ti OR evidence\*:ab,ti OR methodol\*:ab,ti OR quantitativ\*:ab,ti OR analys\*:ab,ti OR assessment\*:ab,ti AND [2003-2012]/py

#1.43

'review'/exp OR review.it OR review:ti AND [2003-2012]/py

#1.42

#1.41 AND [english]/lim AND [2003-2012]/py

#1.41

#1.39 NOT #1.40

#1.40

'child'/exp OR 'newborn'/exp NOT 'adult'/exp

#1.39

#1.23 NOT #1.38

#1.38

#1.24 OR #1.25 OR #1.26 OR #1.27 OR #1.28 OR #1.29 OR #1.30 OR #1.31 OR #1.32 OR #1.33  
OR #1.34 OR #1.35 OR #1.36 OR #1.37  
#1.37  
'rodent'/exp  
#1.36  
'animal model'/exp  
#1.35  
'animal experiment'/exp  
#1.34  
'experimental animal'/exp  
#1.33  
'animals, laboratory'/exp  
#1.32  
'animal studies'/exp  
#1.31  
'nonhuman'/exp  
#1.30  
'animal'/exp NOT ('animal'/exp AND 'human'/exp)  
#1.29  
'case study'/exp  
#1.28  
'case report'/exp  
#1.27  
note:it  
#1.26  
editorial:it  
#1.25  
'letter'/exp  
#1.24  
letter:it  
#1.23  
#1.10 NOT #1.22  
#1.22  
#1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR #1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20  
OR #1.21

#1.21

asthma:ti

#1.20

'asthma'/exp

#1.19

(interstitial NEXT/2 (lung OR pulmonary OR airway\* OR airflow\*)):ti

#1.18

interstitial:ti

#1.17

bronchiolitis:ti OR bronchiectasis:ti

#1.16

'sleep apnea':ti

#1.15

'acute bronchitis':ti

#1.14

cancer:ti OR neoplas\*:ti

#1.13

'lung dysplasia'/exp

#1.12

'sleep apnea syndrome'/exp

#1.11

'bronchial neoplasms'/exp OR 'bronchiectasis'/exp OR 'bronchiolitis'/exp OR 'cystic fibrosis'/exp OR 'lung diseases, interstitial'/exp OR 'lung neoplasms'/exp

#1.10

#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9

#1.9

'chronic bronchitis':ab,ti

#1.8

emphysema:ab,ti

#1.7

'lung emphysema'/exp

#1.6

(chronic NEXT/5 obstruct\*):ti OR (chronic NEXT/5 limit\*):ti

#1.5

'chronic bronchitis'/exp

#1.4

'bronchitis'/exp

#1.3

coad:ab,ti

#1.2

copd:ab,ti

#1.1

'chronic obstructive lung disease'/exp

Mediline

1. exp Pulmonary Disease, Chronic Obstructive/

2. copd.ti,ab.

3. coad.ti,ab.

4. Bronchitis/

5. Chronic bronchitis/

6. (chronic adj5 (obstruct\$ or limit# \$)).ti.

7. (obstruct\$ adj3 (airflow\$ or airway\$ or respirat\$ or lung or pulmonary) adj2 (disease\$ or disorder\$)).ti,ab.

8. Pulmonary emphysema/

9. emphysema.ti,ab.

10. "chronic bronchitis".ti,ab.

11. or/1-10

12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/

13. exp Sleep Apnea Syndromes/

14. Bronchopulmonary Dysplasia/

15. (cancer or neoplas\$).ti.

16. "acute bronchitis".ti.

17. sleep apnea.ti.

18. (bronchiolitis or bronchiectasis).ti.

19. interstitial.ti.

20. (interstitial adj2 (lung or pulmonary or airway\$ or airflow\$)).ti.

21. exp Asthma/

22. asthma.ti.

23. or/12-22
24. 11 not 23
25. letter/
26. editorial/
27. exp historical article/
28. Anecdotes as Topic/
29. comment/
30. case report/
31. animal/ not (animal/ and human/)
32. Animals, Laboratory/
33. exp animal experiment/
34. exp animal model/
35. exp Rodentia/
36. or/25-35
37. 24 not 36
38. limit 37 to english language
39. (exp child/ or exp infant/) not exp adult/
40. 38 not 39
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. double-blind method/ or random allocation/ or single-blind method/
44. exp Clinical Trial/
45. exp Clinical Trials as Topic/
46. clinical trial.pt.
47. random\$.ti,ab.
48. ((clin\$ or control\$) adj5 trial\$).ti,ab.
49. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
50. Placebos/ or placebo\$.ti,ab.
51. (volunteer\$ or "control group" or controls or prospectiv\$).ti,ab.
52. Cross-Over Studies/
53. ((crossover or cross-over or cross over) adj2 (design\$ or stud\$ or procedure\$ or trial\$)).ti,ab.
54. or/41-53
55. "review"/ or review.pt. or review.ti.
56. (systematic or evidence\$ or methodol\$ or quantitativ\$ or analys\$ or assessment\$).ti,sh,ab.

57. 55 and 56
58. meta-analysis.pt.
59. Meta-Analysis/
60. exp Meta-Analysis as Topic/
61. (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$).mp.
62. ((systematic\$ or evidence\$ or methodol\$ or quantitativ\$) adj5 (review\$ or survey\$ or overview\$)).ti,ab,sh.
63. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
64. or/55-63
65. 54 or 64
66. macrolides.mp. or Macrolides/
67. (azithromycin or clarithromycin or dirithromycin or erithromycin or roxithromycin or telithromycin or troleandomycin).ti,ab.
68. Quinolones/ or quinolones.mp.
69. Fluoroquinolones/
70. (ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin).ti,ab.
71. or/66-70
72. 40 and 65 and 71
73. limit 72 to yr="2003 -Current"

#### WP3- COPD Population AND LAMAs/LABAs

Embase

- 137
- #4.118
- #4.110 AND #4.117
- #4.117
- #4.109 AND #4.116
- #4.116
- #4.111 OR #4.112 OR #4.113 OR #4.114 OR #4.115
- #4.115
- exacerbat\*:ab,ti
- #4.114

exacerbation\*:ab,ti

#4.113

(acute NEXT/3 exacerbation\*):ab,ti

#4.112

attack:ab,ti

#4.111

'aggravation':ab,ti

#4.110

#4.109 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim)

#4.109

#4.108 AND [1-8-2009]/sd NOT [2-5-2012]/sd

#4.108

#4.69 AND #4.107

#4.107

#4.86 OR #4.94 OR #4.106

#4.106

#4.95 OR #4.96 OR #4.97 OR #4.98 OR #4.99 OR #4.100 OR #4.101 OR #4.102 OR #4.103 OR #4.104 OR #4.105

#4.105

indacaterol:ab,ti

#4.104

'indacaterol'/exp

#4.103

'budesonide plus formoterol'/exp

#4.102

budesonide:ab,ti OR beclomethasone:ab,ti OR aerobec:ab,ti OR 'asmabeck clickhaler':ab,ti OR 'beclazone easi breathe':ab,ti OR becodisks:ab,ti OR 'cleni modulite':ab,ti OR qvar:ab,ti OR fostair:ab,ti

#4.101

'beclomethasone'/exp

#4.100

flixotide:ab,ti OR accuhaler:ab,ti OR diskhaler:ab,ti OR nebules:ab,ti OR seretide:ab,ti

#4.99

fluticasone:ab,ti

#4.98

'budesonide'/exp

#4.97

glucocorticoid\*:ab,ti OR steroid\*:ab,ti OR corticosteroid\*:ab,ti

#4.96

'glucocorticoid'/exp

#4.95

'corticosteroid'/exp

#4.94

#4.87 OR #4.88 OR #4.89 OR #4.90 OR #4.91 OR #4.92 OR #4.93

#4.93

'anticholinergic bronchodilator':ab,ti

#4.92

tiotropium:ab,ti OR spiriva:ab,ti

#4.91

'tiotropium bromide'/exp

#4.90

(anti\*cholinergic\* NEXT/2 (agent\* OR antagonist\*)):ab,ti

#4.89

(anti\*muscarinic\* NEXT/2 (agent\* OR antagonist\*)):ab,ti

#4.88

'muscarinic receptor blocking agent'/exp

#4.87

'cholinergic receptor blocking agent'/exp

#4.86

#4.70 OR #4.71 OR #4.72 OR #4.73 OR #4.74 OR #4.75 OR #4.76 OR #4.77 OR #4.78 OR #4.79

OR #4.80 OR #4.81 OR #4.82 OR #4.83 OR #4.84 OR #4.85

#4.85

'bronchodilator agent'/exp

#4.84

salmeterol:ab,ti OR serevent:ab,ti OR accuhaler:ab,ti OR evohaler:ab,ti OR diskhaler:ab,ti

#4.83

salmeterol:ab,ti

#4.82

albuterol:ab,ti

#4.81

'albuterol'/exp

#4.80

'atimos modulite':ab,ti OR foradil:ab,ti OR oxis:ab,ti

#4.79

((formoterol OR eformoterol) NEXT/1 fumarate):ab,ti

#4.78

'formoterol fumarate'/exp

#4.77

'formoterol'/exp

#4.76

ethanolamines:ab,ti OR aminoethanols:ab,ti

#4.75

'ethanolamine derivative'/exp

#4.74

'ethanolamine'/exp

#4.73

((agonist\* OR adrenergic) NEXT/3 beta):ti

#4.72

betamimetics:ab,ti

#4.71

((agonist\* OR adrenergic) NEXT/3 beta):ab,ti

#4.70

'beta adrenergic receptor stimulating agent'/exp

#4.69

#4.44 AND #4.68

#4.68

#4.53 OR #4.67

#4.67

#4.54 OR #4.55 OR #4.56 OR #4.57 OR #4.58 OR #4.59 OR #4.60 OR #4.61 OR #4.62 OR #4.63  
OR #4.64 OR #4.65 OR #4.66

#4.66

((crossover OR 'cross over' OR 'cross over') NEXT/2 (design\* OR stud\* OR procedure\* OR  
trial\*)):ab,ti

#4.65

'crossover procedure'/exp

#4.64

((singl\* OR double\* OR triple\* OR treble\*) NEXT/5 (blind\* OR mask\*)):ab,ti

#4.63

random\*:ab,ti

#4.62

placebo:ab,ti

#4.61

'randomization'/exp

#4.60

'clinical article'/exp

#4.59

((clinical\* OR control\* OR compar\*) NEXT/3 (trial\* OR study OR studies)):ab,ti

#4.58

'double blind procedure'/exp

#4.57

'placebo'/exp

#4.56

'clinical study'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'phase 1 clinical trial'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp

#4.55

'clinical trial'/exp

#4.54

'controlled study'/exp OR 'randomized controlled trial'/exp

#4.53

#4.47 OR #4.48 OR #4.49 OR #4.50 OR #4.51 OR #4.52

#4.52

((pool\* OR combined OR combining) NEXT/1 (data OR trials OR studies OR results)):ab,ti

#4.51

((systematic\* OR evidence\* OR methodol\* OR quantitativ\*) NEXT/5 (review\* OR survey\* OR overview\*)):ab,ti

#4.50

'meta-analysis':ab,ti OR metanaly\*:ab,ti OR metaanaly\*:ab,ti OR 'meta analysis':ab,ti

#4.49

'systematic review'/exp

#4.48

'meta analysis'/exp

#4.47

#4.45 AND #4.46

#4.46

systematic:ab,ti OR evidence\*:ab,ti OR methodol\*:ab,ti OR quantitativ\*:ab,ti OR analys\*:ab,ti  
OR assessment\*:ab,ti

#4.45

'review'/exp OR review.it OR review:ti

#4.44

#4.43 AND [2009-2012]/py

#4.43

#4.42 AND [english]/lim

#4.42

#4.40 NOT #4.41

#4.41

'child'/exp OR 'newborn'/exp NOT 'adult'/exp

#4.40

#4.24 NOT #4.39

#4.39

#4.25 OR #4.26 OR #4.27 OR #4.28 OR #4.29 OR #4.30 OR #4.31 OR #4.32 OR #4.33 OR #4.34  
OR #4.35 OR #4.36 OR #4.37 OR #4.38

#4.38

'rodent'/exp

#4.37

'animal model'/exp

#4.36

'animal experiment'/exp

#4.35

'experimental animal'/exp

#4.34

'animals, laboratory'/exp

#4.33

'animal studies'/exp

#4.32

'nonhuman'/exp

#4.31

'animal'/exp NOT ('animal'/exp AND 'human'/exp)

#4.30

'case study'/exp

#4.29

'case report'/exp

#4.28

note:it

#4.27

editorial:it

#4.26

'letter'/exp

#4.25

letter:it

#4.24

#4.19 NOT #4.23

#4.23

#4.11 OR #4.12 OR #4.13 OR #4.14 OR #4.15 OR #4.16 OR #4.17 OR #4.18 OR #4.20 OR #4.21  
OR #4.22

#4.22

asthma:ti

#4.21

'asthma'/exp

#4.20

(interstitial NEXT/2 (lung OR pulmonary OR airway\* OR airflow\*)):ti

#4.19

#4.1 OR #4.2 OR #4.3 OR #4.4 OR #4.5 OR #4.6 OR #4.7 OR #4.8 OR #4.9 OR #4.10

#4.18

interstitial:ti

#4.17

bronchiolitis:ti OR bronchiectasis:ti

#4.16

'sleep apnea':ti

#4.15

'acute bronchitis':ti

#4.14

cancer:ti OR neoplas\*:ti

#4.13

'lung dysplasia'/exp

#4.12

'sleep apnea syndrome'/exp

#4.11

'bronchial neoplasms'/exp OR 'bronchiectasis'/exp OR 'bronchiolitis'/exp OR 'cystic fibrosis'/exp OR 'lung diseases, interstitial'/exp OR 'lung neoplasms'/exp

#4.10

'chronic bronchitis':ab,ti

#4.9

emphysema:ab,ti

#4.8

'lung emphysema'/exp

#4.7

(obstruct\* NEXT/3 airflow\*):ab,ti OR (obstruct\* NEXT/3 airway\*):ab,ti OR (obstruct\* NEXT/3 respirat\*):ab,ti OR (obstruct\* NEXT/3 lung):ab,ti OR (obstruct\* NEXT/3 pulmonary):ab,ti

#4.6

(chronic NEXT/5 obstruct\*):ti OR (chronic NEXT/5 limit\*):ti

#4.5

'chronic bronchitis'/exp

#4.4

'bronchitis'/exp

#4.3

coad:ab,ti

#4.2

copd:ab,ti

#4.1

'chronic obstructive lung disease'/exp

## Medline

1. exp Pulmonary Disease, Chronic Obstructive/
2. copd.ti,ab.
3. coad.ti,ab.
4. Bronchitis/
5. Chronic bronchitis/
6. (chronic adj5 (obstruct\$ or limit#\$\$)).ti.
7. (obstruct\$ adj3 (airflow\$ or airway\$ or respirat\$ or lung or pulmonary) adj2 (disease\$ or disorder\$)).ti,ab.
8. Pulmonary emphysema/
9. emphysema.ti,ab.
10. "chronic bronchitis".ti,ab.
11. or/1-10
12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
13. exp Sleep Apnea Syndromes/
14. Bronchopulmonary Dysplasia/
15. (cancer or neoplas\$).ti.
16. "acute bronchitis".ti.
17. sleep apnea.ti.
18. (bronchiolitis or bronchiectasis).ti.
19. interstitial.ti.
20. (interstitial adj2 (lung or pulmonary or airway\$ or airflow\$)).ti.
21. exp Asthma/
22. asthma.ti.
23. or/12-22
24. 11 not 23
25. letter/
26. editorial/
27. exp historical article/
28. Anecdotes as Topic/
29. comment/
30. case report/

31. animal/ not (animal/ and human/)
32. Animals, Laboratory/
33. exp animal experiment/
34. exp animal model/
35. exp Rodentia/
36. or/25-35
37. 24 not 36
38. limit 37 to english language
39. (exp child/ or exp infant/) not exp adult/
40. 38 not 39
41. exp Pulmonary Disease, Chronic Obstructive/
42. copd.ti,ab.
43. coad.ti,ab.
44. Bronchitis/
45. Chronic bronchitis/
46. (chronic adj5 (obstruct\$ or limit#\$)).ti.
47. (obstruct\$ adj3 (airflow\$ or airway\$ or respirat\$ or lung or pulmonary) adj2 (disease\$ or disorder\$)).ti,ab.
48. Pulmonary emphysema/
49. emphysema.ti,ab.
50. "chronic bronchitis".ti,ab.
51. or/41-50
52. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
53. exp Sleep Apnea Syndromes/
54. Bronchopulmonary Dysplasia/
55. (cancer or neoplas\$).ti.
56. "acute bronchitis".ti.
57. sleep apnea.ti.
58. (bronchiolitis or bronchiectasis).ti.
59. interstitial.ti.
60. (interstitial adj2 (lung or pulmonary or airway\$ or airflow\$)).ti.
61. exp Asthma/
62. asthma.ti.
63. or/52-62

64. 51 not 63
65. letter/
66. editorial/
67. exp historical article/
68. Anecdotes as Topic/
69. comment/
70. case report/
71. animal/ not (animal/ and human/)
72. Animals, Laboratory/
73. exp animal experiment/
74. exp animal model/
75. exp Rodentia/
76. or/65-75
77. 64 not 76
78. limit 77 to english language
79. (exp child/ or exp infant/) not exp adult/
80. 78 not 79
81. "review"/ or review.pt. or review.ti.
82. (systematic or evidence\$ or methodol\$ or quantitativ\$ or analys\$ or assessment\$).ti,sh,ab.
83. 81 and 82
84. meta-analysis.pt.
85. Meta-Analysis/
86. exp Meta-Analysis as Topic/
87. (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$).mp.
88. ((systematic\$ or evidence\$ or methodol\$ or quantitativ\$) adj5 (review\$ or survey\$ or overview\$)).ti,ab,sh.
89. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
90. or/83-89
91. randomized controlled trial.pt.
92. controlled clinical trial.pt.
93. double-blind method/ or random allocation/ or single-blind method/
94. exp Clinical Trial/
95. exp Clinical Trials as Topic/
96. clinical trial.pt.
97. random\$.ti,ab.

98. ((clin\$ or control\$) adj5 trial\$).ti,ab.
99. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
100. Placebos/ or placebo\$.ti,ab.
101. (volunteer\$ or "control group" or controls or prospectiv\$).ti,ab.
102. Cross-Over Studies/
103. ((crossover or cross-over or cross over) adj2 (design\$ or stud\$ or procedure\$ or trial\$)).ti,ab.
104. or/91-103
105. 90 or 104
106. 80 and 105
107. cholinergic antagonists/
108. muscarinic antagonists/
109. (anti?muscarinic\$ adj2 (agent\$ or antagonist\$)).ti,ab.
110. (anti?cholinergic\$ adj2 (agent\$ or antagonist\$)).ti,ab.
111. anticholinergic bronchodilator\$.ti,ab.
112. bronchodilator agents/
113. (bronchodilat\$ adj2 (drug\$ or agent\$)).ti,ab.
114. (broncholytic\$ adj2 (drug\$ or agent\$)).ti,ab.
115. or/107-114
116. (tiotropium or spiriva or respimat).ti,ab.
117. ipratropium bromide/
118. (ipratropium or atrovent or aerocaps).ti,ab.
119. or/116-118
120. 115 or 119
121. 106 and 120
122. limit 121 to yr="2003 -Current"

### WP3- COPD Population AND Mucolytics

Embase

43

#1.61

#1.43 AND #1.60

#1.60

#1.44 OR #1.45 OR #1.46 OR #1.47 OR #1.48 OR #1.49 OR #1.50 OR #1.51 OR #1.52 OR #1.53  
OR #1.54 OR #1.55 OR #1.56 OR #1.57 OR #1.58 OR #1.59

#1.59

(mucolytic\* NEAR/2 (agent\* OR drug\*)):ab,ti

#1.58

mucinolytic\*:ab,ti

#1.57

acetylcysteine:ab,ti OR 'acetyl cystein':ab,ti OR 'acetyl cysteine':ab,ti OR acetylcystein:ab,ti OR 'acetyl i cysteine':ab,ti

#1.56

'acetylcysteine'/exp

#1.55

erdosteine:ab,ti OR dithiosteine:ab,ti OR erdotin:ab,ti

#1.54

'erdosteine'/exp

#1.53

mecysteine:ab,ti OR 'cysteine methylester':ab,ti OR 'cysteine methly ester':ab,ti OR visclair:ab,ti OR 'methyl cysteine':ab,ti OR methylcysteine:ab,ti

#1.52

'mecysteine'/exp

#1.51

carbocisteine:ab,ti OR carbocistine:ab,ti OR carbocysteine:ab,ti OR carboxymethylcysteine:ab,ti

#1.50

carbocisteine:ab,ti

#1.49

'carbocisteine'/exp

#1.48

'secretolytic agent':ab,ti OR 'secretolytic agents':ab,ti

#1.47

'mucociliary clearance':ab,ti

#1.46

mucolytic\*:ab,ti

#1.45

'mucolytic agent'/exp

#1.44

'expectorant agent'/exp

#1.43

#1.42 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [english]/lim AND [2009-2012]/py

#1.42

#1.41 AND [english]/lim AND [2009-2012]/py

#1.41

#1.39 NOT #1.40

#1.40

'child'/exp OR 'newborn'/exp NOT 'adult'/exp

#1.39

#1.23 NOT #1.38

#1.38

#1.24 OR #1.25 OR #1.26 OR #1.27 OR #1.28 OR #1.29 OR #1.30 OR #1.31 OR #1.32 OR #1.33 OR #1.34 OR #1.35 OR #1.36 OR #1.37

#1.37

'rodent'/exp

#1.36

'animal model'/exp

#1.35

'animal experiment'/exp

#1.34

'experimental animal'/exp

#1.33

'animals, laboratory'/exp

#1.32

'animal studies'/exp

#1.31

'nonhuman'/exp

#1.30

'animal'/exp NOT ('animal'/exp AND 'human'/exp)

#1.29

'case study'/exp

#1.28

'case report'/exp

#1.27

note:it

#1.26

editorial:it

#1.25

'letter'/exp

#1.24

letter:it

#1.23

#1.10 NOT #1.22

#1.22

#1.11 OR #1.12 OR #1.13 OR #1.14 OR #1.15 OR #1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20  
OR #1.21

#1.21

asthma:ti

#1.20

'asthma'/exp

#1.19

(interstitial NEXT/2 (lung OR pulmonary OR airway\* OR airflow\*)):ti

#1.18

interstitial:ti

#1.17

bronchiolitis:ti OR bronchiectasis:ti

#1.16

'sleep apnea':ti

#1.15

'acute bronchitis':ti

#1.14

cancer:ti OR neoplas\*:ti

#1.13

'lung dysplasia'/exp

#1.12

'sleep apnea syndrome'/exp

#1.11

'bronchial neoplasms'/exp OR 'bronchiectasis'/exp OR 'bronchiolitis'/exp OR 'cystic fibrosis'/exp OR 'lung diseases, interstitial'/exp OR 'lung neoplasms'/exp

#1.10

#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9

#1.9

'chronic bronchitis':ab,ti

#1.8

emphysema:ab,ti

#1.7

'lung emphysema'/exp

#1.6

(chronic NEXT/5 obstruct\*):ti OR (chronic NEXT/5 limit\*):ti

#1.5

'chronic bronchitis'/exp

#1.4

'bronchitis'/exp

#1.3

coad:ab,ti

#1.2

copd:ab,ti

#1.1

'chronic obstructive lung disease'/exp

Medline

1. expectorants/

2. mucolytic\$.ti,ab.

3. (mucolytic\$ adj2 (agent\$ or drug\$)).ti,ab.

4. mucinolytic\$.ti,ab.

5. mucociliary clearance.ti,ab.

6. secretolytic agent\$.ti,ab.

7. carbocysteine.ti,ab.

8. (carbocysteine or carbocistine or carbocysteine or carboxymethylcysteine).ti,ab.

9. (mecysteine or cysteine methylester or cysteine methyl ester or visclair or methyl cysteine or methylcysteine).ti,ab.

10. (erdosteine or dithiosteine or erdotin).ti,ab.
11. (acetylcysteine or acetyl cystein or acetylcystein or acetyl cysteine or acetylcysteine or acetyl I cysteine).ti,ab.
12. acetylcysteine/
13. or/1-12
14. exp Pulmonary Disease, Chronic Obstructive/
15. copd.ti,ab.
16. coad.ti,ab.
17. Bronchitis/
18. Chronic bronchitis/
19. (chronic adj5 (obstruct\$ or limit#\$)).ti.
20. (obstruct\$ adj3 (airflow\$ or airway\$ or respirat\$ or lung or pulmonary) adj2 (disease\$ or disorder\$)).ti,ab.
21. Pulmonary emphysema/
22. emphysema.ti,ab.
23. "chronic bronchitis".ti,ab.
24. or/14-23
25. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
26. exp Sleep Apnea Syndromes/
27. Bronchopulmonary Dysplasia/
28. (cancer or neoplas\$).ti.
29. "acute bronchitis".ti.
30. sleep apnea.ti.
31. (bronchiolitis or bronchiectasis).ti.
32. interstitial.ti.
33. (interstitial adj2 (lung or pulmonary or airway\$ or airflow\$)).ti.
34. exp Asthma/
35. asthma.ti.
36. or/25-35
37. 24 not 36
38. letter/
39. editorial/
40. exp historical article/
41. Anecdotes as Topic/

42. comment/
43. case report/
44. animal/ not (animal/ and human/)
45. Animals, Laboratory/
46. exp animal experiment/
47. exp animal model/
48. exp Rodentia/
49. or/38-48
50. 37 not 49
51. limit 50 to english language
52. (exp child/ or exp infant/) not exp adult/
53. 51 not 52
54. randomized controlled trial.pt.
55. controlled clinical trial.pt.
56. double-blind method/ or random allocation/ or single-blind method/
57. exp Clinical Trial/
58. exp Clinical Trials as Topic/
59. clinical trial.pt.
60. random\$.ti,ab.
61. ((clin\$ or control\$) adj5 trial\$).ti,ab.
62. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
63. Placebos/ or placebo\$.ti,ab.
64. (volunteer\$ or "control group" or controls or prospectiv\$).ti,ab.
65. Cross-Over Studies/
66. ((crossover or cross-over or cross over) adj2 (design\$ or stud\$ or procedure\$ or trial\$)).ti,ab.
67. or/54-66
68. "review"/ or review.pt. or review.ti.
69. (systematic or evidence\$ or methodol\$ or quantitativ\$ or analys\$ or assessment\$).ti,sh,ab.
70. 68 and 69
71. meta-analysis.pt.
72. Meta-Analysis/
73. exp Meta-Analysis as Topic/
74. (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$).mp.

75. ((systematic\$ or evidence\$ or methodol\$ or quantitativ\$) adj5 (review\$ or survey\$ or overview\$)).ti,ab,sh.

76. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.

77. or/70-76

78. 67 or 77

79. 13 and 53 and 78

80. limit 79 to yr="2009 -Current"

WP3- COPD Population AND PDEIVs

Embase

#3.75

#3.74 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2003-2012]/py

#3.74

#3.67 AND #3.73

#3.73

#3.68 OR #3.69 OR #3.70 OR #3.71 OR #3.72

#3.72

rolipram:ab,ti OR cilomilast:ab,ti OR ariflo:ab,ti OR sb207499:ab,ti OR telomilast:ab,ti OR oric485:ab,ti OR oglemilast:ab,ti OR 'grc 3886':ab,ti OR qak423:ab,ti OR arofylline:ab,ti OR 'awd12 281':ab,ti

#3.71

roflumilast:ab,ti

#3.70

'pde iv':ab,ti

#3.69

'phosphodiesterase iv inhibitor'/exp

#3.68

'roflumilast'/exp OR roflumilast

#3.67

#3.42 AND #3.66

#3.66

#3.51 OR #3.65

#3.65

#3.52 OR #3.53 OR #3.54 OR #3.55 OR #3.56 OR #3.57 OR #3.58 OR #3.59 OR #3.60 OR #3.61  
OR #3.62 OR #3.63 OR #3.64

#3.64

((crossover OR 'cross over' OR 'cross over') NEXT/2 (design\* OR stud\* OR procedure\* OR  
trial\*)):ab,ti AND [2003-2012]/py

#3.63

'crossover procedure'/exp AND [2003-2012]/py

#3.62

((singl\* OR double\* OR triple\* OR treble\*) NEXT/5 (blind\* OR mask\*)):ab,ti AND [2003-  
2012]/py

#3.61

random\*:ab,ti AND [2003-2012]/py

#3.60

placebo:ab,ti AND [2003-2012]/py

#3.59

'randomization'/exp AND [2003-2012]/py

#3.58

'clinical article'/exp AND [2003-2012]/py

#3.57

((clinical\* OR control\* OR compar\*) NEXT/3 (trial\* OR study OR studies)):ab,ti AND [2003-  
2012]/py

#3.56

'double blind procedure'/exp AND [2003-2012]/py

#3.55

'placebo'/exp AND [2003-2012]/py

#3.54

'clinical study'/exp OR 'major clinical study'/exp OR 'clinical trial'/exp OR 'phase 1 clinical  
trial'/exp OR 'phase 2 clinical trial'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical  
trial'/exp AND [2003-2012]/py

#3.53

'clinical trial'/exp AND [2003-2012]/py

#3.52

'controlled study'/exp OR 'randomized controlled trial'/exp AND [2003-2012]/py

#3.51

#3.45 OR #3.46 OR #3.47 OR #3.48 OR #3.49 OR #3.50

#3.50

((pool\* OR combined OR combining) NEXT/1 (data OR trials OR studies OR results)):ab,ti AND [2003-2012]/py

#3.49

((systematic\* OR evidence\* OR methodol\* OR quantitativ\*) NEXT/5 (review\* OR survey\* OR overview\*)):ab,ti AND [2003-2012]/py

#3.48

'meta-analysis':ab,ti OR metanaly\*:ab,ti OR metaanaly\*:ab,ti OR 'meta analysis':ab,ti AND [2003-2012]/py

#3.47

'systematic review'/exp AND [2003-2012]/py

#3.46

'meta analysis'/exp AND [2003-2012]/py

#3.45

#3.43 AND #3.44

#3.44

systematic:ab,ti OR evidence\*:ab,ti OR methodol\*:ab,ti OR quantitativ\*:ab,ti OR analys\*:ab,ti OR assessment\*:ab,ti AND [2003-2012]/py

#3.43

'review'/exp OR review.it OR review:ti AND [2003-2012]/py

#3.42

#3.41 AND [english]/lim AND [2003-2012]/py

#3.41

#3.39 NOT #3.40

#3.40

'child'/exp OR 'newborn'/exp NOT 'adult'/exp

#3.39

#3.23 NOT #3.38

#3.38

#3.24 OR #3.25 OR #3.26 OR #3.27 OR #3.28 OR #3.29 OR #3.30 OR #3.31 OR #3.32 OR #3.33 OR #3.34 OR #3.35 OR #3.36 OR #3.37

#3.37

'rodent'/exp

#3.36

'animal model'/exp

#3.35

'animal experiment'/exp

#3.34

'experimental animal'/exp

#3.33

'animals, laboratory'/exp

#3.32

'animal studies'/exp

#3.31

'nonhuman'/exp

#3.30

'animal'/exp NOT ('animal'/exp AND 'human'/exp)

#3.29

'case study'/exp

#3.28

'case report'/exp

#3.27

note:it

#3.26

editorial:it

#3.25

'letter'/exp

#3.24

letter:it

#3.23

#3.10 NOT #3.22

#3.22

#3.11 OR #3.12 OR #3.13 OR #3.14 OR #3.15 OR #3.16 OR #3.17 OR #3.18 OR #3.19 OR #3.20  
OR #3.21

#3.21

asthma:ti

#3.20

'asthma'/exp

#3.19

(interstitial NEXT/2 (lung OR pulmonary OR airway\* OR airflow\*)):ti

#3.18

interstitial:ti

#3.17

bronchiolitis:ti OR bronchiectasis:ti

#3.16

'sleep apnea':ti

#3.15

'acute bronchitis':ti

#3.14

cancer:ti OR neoplas\*:ti

#3.13

'lung dysplasia'/exp

#3.12

'sleep apnea syndrome'/exp

#3.11

'bronchial neoplasms'/exp OR 'bronchiectasis'/exp OR 'bronchiolitis'/exp OR 'cystic fibrosis'/exp OR 'lung diseases, interstitial'/exp OR 'lung neoplasms'/exp

#3.10

#3.1 OR #3.2 OR #3.3 OR #3.4 OR #3.5 OR #3.6 OR #3.7 OR #3.8 OR #3.9

#3.9

'chronic bronchitis':ab,ti

#3.8

emphysema:ab,ti

#3.7

'lung emphysema'/exp

#3.6

(chronic NEXT/5 obstruct\*):ti OR (chronic NEXT/5 limit\*):ti

#3.5

'chronic bronchitis'/exp

#3.4

'bronchitis'/exp

#3.3

coad:ab,ti

#3.2

copd:ab,ti

#3.1

'chronic obstructive lung disease'/exp

Medline

1. exp Pulmonary Disease, Chronic Obstructive/
2. copd.ti,ab.
3. coad.ti,ab.
4. Bronchitis/
5. Chronic bronchitis/
6. (chronic adj5 (obstruct\$ or limit#\$)).ti.
7. (obstruct\$ adj3 (airflow\$ or airway\$ or respirat\$ or lung or pulmonary) adj2 (disease\$ or disorder\$)).ti,ab.
8. Pulmonary emphysema/
9. emphysema.ti,ab.
10. "chronic bronchitis".ti,ab.
11. or/1-10
12. bronchial neoplasms/ or exp bronchiectasis/ or exp bronchiolitis/ or cystic fibrosis/ or lung diseases, interstitial/ or lung neoplasms/
13. exp Sleep Apnea Syndromes/
14. Bronchopulmonary Dysplasia/
15. (cancer or neoplas\$).ti.
16. "acute bronchitis".ti.
17. sleep apnea.ti.
18. (bronchiolitis or bronchiectasis).ti.
19. interstitial.ti.
20. (interstitial adj2 (lung or pulmonary or airway\$ or airflow\$)).ti.
21. exp Asthma/
22. asthma.ti.
23. or/12-22
24. 11 not 23
25. letter/
26. editorial/
27. exp historical article/

28. Anecdotes as Topic/
29. comment/
30. case report/
31. animal/ not (animal/ and human/)
32. Animals, Laboratory/
33. exp animal experiment/
34. exp animal model/
35. exp Rodentia/
36. or/25-35
37. 24 not 36
38. limit 37 to english language
39. (exp child/ or exp infant/) not exp adult/
40. 38 not 39
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. double-blind method/ or random allocation/ or single-blind method/
44. exp Clinical Trial/
45. exp Clinical Trials as Topic/
46. clinical trial.pt.
47. random\$.ti,ab.
48. ((clin\$ or control\$) adj5 trial\$).ti,ab.
49. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
50. Placebos/ or placebo\$.ti,ab.
51. (volunteer\$ or "control group" or controls or prospectiv\$).ti,ab.
52. Cross-Over Studies/
53. ((crossover or cross-over or cross over) adj2 (design\$ or stud\$ or procedure\$ or trial\$)).ti,ab.
54. or/41-53
55. "review"/ or review.pt. or review.ti.
56. (systematic or evidence\$ or methodol\$ or quantitativ\$ or analys\$ or assessment\$).ti,sh,ab.
57. 55 and 56
58. meta-analysis.pt.
59. Meta-Analysis/
60. exp Meta-Analysis as Topic/
61. (meta-analy\$ or metanaly\$ or metaanaly\$ or meta analy\$).mp.

62. ((systematic\$ or evidence\$ or methodol\$ or quantitativ\$) adj5 (review\$ or survey\$ or overview\$)).ti,ab,sh.
63. ((pool\$ or combined or combining) adj (data or trials or studies or results)).ti,ab.
64. or/55-63
65. 54 or 64
66. roflumilast.ti,ab.
67. Phosphodiesterase 4 Inhibitors/
68. PDE-IV.ti,ab.
69. PDEIV.ti,ab.
70. PDE-IV.hw,mp.
71. rolipram.ti,ab.
72. cilomilast.ti,ab.
73. ariflo.ti,ab.
74. SB207499.ti,ab.
75. telomilast.ti,ab.
76. ORIC485.ti,ab.
77. oglemilast.ti,ab.
78. GRC-3886.ti,ab.
79. QAK423.ti,ab.
80. arofylline.ti,ab.
81. AWD12-281.ti,ab.
82. or/66-81
83. 40 and 65 and 82

### **Study selection**

The lead methodologist screened the titles and abstracts of the retrieved studies and excluded studies on the basis of the pre-defined study selection criteria shown in the online supplement. For those studies that could not be excluded by the title and abstract, we obtained the full text of the studies and then included or excluded the studies on the basis of our full text review. In cases of uncertainty, the opinions of the co-chairs and panellists were obtained and decisions were reached by discussion and consensus. We also screened the reference lists from recent and well-conducted systematic reviews, in order to ensure that our literature review had not missed any relevant studies.

The quality of studies was rated according to the following table:



hospitalizations 20%, and adverse events 15%. They also included the following absolute reduction: St. George's Respiratory Questionnaire score change of 4 points.

### **Formulating and grading recommendations**

The evidence profiles were sent to the guideline panel members for review. Using an iterative consensus process conducted primarily by email, but also via teleconference and face-to-face meetings, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects, cost) of the intervention, the quality of evidence, patient values and preferences, and feasibility (16).

A strong recommendation would have been made for an intervention if the panel was certain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweigh the desirable consequences. A strong recommendation would have indicated that most well-informed patients would choose to have or not to have the intervention.

A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a conditional recommendation was made against an intervention if the panel was uncertain that the undesirable consequences of the intervention outweigh the desirable consequences. Reasons for uncertainty included low or very low overall quality of evidence (determined from the outcomes a priori defined as "critical"), the desirable and undesirable consequences being finely balanced, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not have the intervention.

### **Manuscript preparation**

The initial draft of the manuscript was prepared by the co-chairs, methodologists, and one panellist (MM). The lead methodologist wrote the content for the online supplement, which was edited by the co-chairs. Both the manuscript and the online supplement were reviewed, edited, and approved by all panel members prior to submission.

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