

APPENDIX 1: Search Strategy

Search conducted March 8 and 9, 2005

Databases	#	Keywords	
PubMed Results: 51	1	(copd OR "pulmonary disease, chronic obstructive"[MeSH] OR chronic obstructive pulmonary disease* OR chronic obstructive lung disease*)	
	2	#1 NOT asthma	
	3	(beta agonist* OR "Adrenergic beta-Agonists"[MeSH] OR long acting beta-2 agonist* OR long acting bronchodilator* OR formoterol OR salmeterol)	
	4	(corticosteroid* OR "Adrenal Cortex Hormones"[MeSH] OR fluticasone OR budesonide OR advair OR symbicort)	
	5	#2 AND #3 AND #4	
	6	2000/01/01 AND (clinical trial OR meta-analysis OR randomized controlled trial OR review)	
Medline <1999 to February week 4 2005> Results: 52	1	copd.mp. or exp Pulmonary Disease, Chronic Obstructive/	
	2	chronic obstructive pulmonary disease\$.mp	
	3	chronic obstructive lung disease\$.mp	
	4	or/1-3	
	5	4 not asthma.mp	
	6	exp Adrenergic beta-Agonists/ or beta agonist\$.mp	
	7	long acting beta-2 agonist\$.mp	
	8	long acting bronchodilator\$.mp	
	9	formoterol.mp	
	10	salmeterol.mp	
	13	or/6-10	
	14	(salmeterol and fluticasone).mp	
	15	(budesonide and formoterol).mp	
	16	advair.mp	
	17	symbicort.mp	
	18	corticosteroid\$.mp. or exp Adrenal Cortex Hormones/	
	19	or/12-16	
	20	5 and 11 and 17	
	21	limit 18 to (yr=2000 - 2005 and (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial or "review"))	
	HealthSTAR <1987 to November 2004> Results: 40	1	copd.mp. or exp Lung Diseases, Obstructive/
		2	chronic obstructive pulmonary disease\$.mp.
3		chronic obstructive lung disease\$.mp.	
4		or/1-3	
5		4 not asthma.mp.	
6		exp Adrenergic beta-Agonists/ or beta agonist\$.mp.	
7		long acting beta-2 agonist\$.mp.	
8		long acting bronchodilator\$.mp.	
9		formoterol.mp.	
10		salmeterol.mp.	
11		or/6-10	
12		(salmeterol and fluticasone).mp.	
13		(budesonide and formoterol).mp.	
14		advair.mp.	
15		symbicort.mp.	
16		corticosteroid\$.mp. or exp Adrenal Cortex Hormones/	
17		or/12-16	
18		5 and 11 and 17	

Databases	#	Keywords
	19	limit 18 to (yr=2000 - 2005 and (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or evaluation studies or meta analysis or randomized controlled trial or "review"))
EBM Reviews – Database of Abstracts of Reviews of Effects <1 st Quarter 2005> Results: 2	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18	1 copd.mp. 2 chronic obstructive pulmonary disease\$.mp. 3 chronic obstructive lung disease\$.mp. 4 or/1-3 5 4 not asthma.mp. 6 beta agonist\$.mp. 7 long acting beta-2 agonist\$.mp. 8 long acting bronchodilator\$.mp. 9 formoterol.mp. 10 salmeterol.mp. 11 or/6-10 12 (salmeterol and fluticasone).mp. 13 (budesonide and formoterol).mp. 14 advair.mp. 15 symbicort.mp. 16 corticosteroid\$.mp. 17 or/12-16 18 5 and 11 and 17
EBM Reviews – Cochrane Central Register of Controlled Trials <1 st Quarter 2005> Results: 53	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19	1 copd.mp. 2 chronic obstructive pulmonary disease\$.mp. 3 chronic obstructive lung disease\$.mp. 4 or/1-3 5 4 not asthma.mp. 6 beta agonist\$.mp. 7 long acting beta-2 agonist\$.mp. 8 long acting bronchodilator\$.mp. 9 formoterol.mp. 10 salmeterol.mp. 11 or/6-10 12 (salmeterol and fluticasone).mp. 13 (budesonide and formoterol).mp. 14 advair.mp. 15 symbicort.mp. 16 corticosteroid\$.mp. 17 or/12-16 18 5 and 11 and 17 19 limit 18 to (yr=2000 – 2004)
International Pharmaceutical Abstracts <1970 to February 2005> Results: 21	1 2 3 4 5 6 7 8 9 10 11 12 13 14	1 copd.mp. or exp Lung Diseases, Obstructive/ 2 chronic obstructive pulmonary disease\$.mp. 3 chronic obstructive lung disease\$.mp. 4 or/1-3 5 4 not asthma.mp. 6 exp Adrenergic beta-Agonists/ or beta agonist\$.mp. 7 long acting beta-2 agonist\$.mp. 8 long acting bronchodilator\$.mp. 9 formoterol.mp. 10 salmeterol.mp. 11 or/6-10 12 (salmeterol and fluticasone).mp. 13 (budesonide and formoterol).mp. 14 advair.mp.

Databases	#	Keywords
	15	sybicort.mp.
	16	corticosteroid\$.mp.
	17	or/12-16
	18	5 and 11 and 17
EMBASE <1996 to 2005 week 10> Results: 78	1	copd.mp. or exp Chronic Obstructive Lung Disease/
	2	chronic obstructive pulmonary disease\$.mp.
	3	chronic obstructive lung disease\$.mp.
	4	or/1-3
	5	4 not asthma.mp.
	6	exp Beta Adrenergic Receptor Stimulating Agent/ or beta agonist\$.mp.
	7	long acting beta-2 agonist\$.mp.
	8	long acting bronchodilator\$.mp.
	9	formoterol.mp. OR exp FORMOTEROL/
	10	salmeterol.mp. OR exp SALMETEROL/
	11	or/6-10
	12	(salmeterol and fluticasone).mp. OR exp FLUTICASONE PORPIONATE PLUS SALMETEROL
	13	(budesonide and formoterol).mp. OR exp BUDESONIDE PLUS FORMOTEROL
	14	advair.mp.
	15	sybicort.mp.
	16	or/12-15
	17	5 and 11 and 16
	18	clinical trial/ OR (clin\$adj25 trial\$.ti,ab OR randomized controlled trial/ OR randomised controlled trial\$.mp OR controlled clinical trial\$.mp OR random allocation.mp OR exp randomization OR exp comparative study/ OR evaluation research.mp
	19	17 and 18
	20	limit 19 to yr=2000-2005
Centre for Reviews and Dissemination (DARE, NHS EED, HTA) Results: 6 Web of Science Results: 26	1	(copd OR chronic obstructive pulmonary disease OR chronic obstructive lung disease) AND (beta agonists OR long acting beta agonist OR formoterol OR salmeterol) AND (corticosteroids OR fluticasone OR budesonide OR advair OR sybicort OR seritide)
	1	TS=(copd OR chronic obstructive pulmonary disease* OR chronic obstructive lung disease*)
	2	TS= asthma
	3	#1 NOT #2
	4	TS=(beta agonist* OR long acting beta-2 agonist* OR long acting bronchodilator* OR formoterol OR salmeterol)
	5	TS=(fluticasone OR budesonide OR advair OR sybicort OR seritide OR corticosteroid*)
	6	#3 AND #4 AND #5
	7	TS=(randomized controlled trial* OR clinical controlled trial* OR clinical trial* OR meta-analysis OR systematic review* OR meta-analyses)
	8	#6 AND #7

Total: 319 references

Removed: 156 duplicates

Remaining: 163 references

APPENDIX 2: Quality Assessment

Study Quality

Reference Manager number: _____ Reviewer _____

Randomization total points: 0, 1, 2

A trial reporting that it is randomized receives one point.

Trials describing an appropriate method of randomization (table of random numbers, computer generated) receive an additional point.

If the report describes the trial as randomized, and uses an inappropriate method of randomization (date of birth, hospital numbers), a point is deducted.

Double-blinding total points: 0, 1, 2

A trial reporting that it is double-blind receives one point. Trials that describe an appropriate method of double-blinding (identical placebo, active placebo) receive an additional point. If the report describes the trial as double-blind, and uses an inappropriate method (e.g., comparison of tablets versus injection with no double dummy), a point is deducted.

Withdrawals and dropouts total points: 0, 1

A trial reporting the number and reason for withdrawals receives one point. If there is no statement, no point is given.

Total score: low (zero to two points), moderate (three to four points), high (five points)

Allocation concealment: adequate, inadequate, unclear

Adequate: central randomization; numbered or coded bottles or containers; drugs prepared by a pharmacy; serially numbered, opaque, sealed envelopes

Inadequate: alternation; reference to case record number, or date of birth

Unclear: allocation concealment approach is not reported or fits neither of the above categories.

APPENDIX 3: Data Extraction Form

Data Extraction Form	
Inclusion criteria	
Subjects	
<ol style="list-style-type: none"> 1. chronic obstructive pulmonary disease (COPD) 2. forced expiratory volume (FEV₁) <80% predicted 3. FEV₁/forced vital capacity (FVC) <70% 4. non-asthmatic subjects 	
Trials	
<ol style="list-style-type: none"> 1. prospective randomized controlled trial (RCT) 2. blinded 3. parallel and crossover 	
Types of interventions	
<ol style="list-style-type: none"> 1. trial of inhaled long-acting β_2-agonists (LABA) plus inhaled corticosteroids (ICS) administered as monocomponent simultaneously or as combination ICS-LABA inhaler versus inhaled LABA alone for at least three months; no restrictions placed on dosage 	
Outcome measurements	
<ol style="list-style-type: none"> 1. exacerbation rates 2. death rates 	
Did not have deaths as primary endpoint but did measure exacerbations.	

Data Extraction Sheet	
Reviewer's initials: _____	
Study Number	
Reference	
Industry sponsored	
Randomized controlled	
Randomization (central)	
Randomization (unclear) yes or no	
Blinding	
Double-blind	
Study type	
Other COPD medications allowed [short-acting β -agonist (SABA), ipratropium, theophylline, teotropium]	
Study groups [(budesonide, formoterol, placebo, budesonide+formoterol), (fluticasone, salmeterol, placebo, futicasone+salmeterol)]	
HRQL score included (yes or no)	
HRQL used [SGRQ, CRQ, SF-36, 15D, other (list)]	

Data Extraction Table				
Parameters	Placebo	LABA	LABA/ICS	Total patients
Dose and frequency				
Length of run-in period				
Duration of study treatment				
Number of patients: Screened				
Eligible				
Randomized				
Completed				
Number of dropouts:				
Male (% randomized)				
Mean age				
Smokers (% randomized)				
Current (%)				
Mean pack years				
Years since dx* COPD				
Mean FEV ₁ (+SD)				
Mean FEV ₁ (% predicted)				
FEV ₁ range (% predicted)				
Mean FEV ₁ /FVC (absolute)				
Mean FVC (+SD)				
Mean FVC (% predicted)				
FEV ₁ reversibility (reported yes or no)				
% reversibility FEV ₁				
Continuous home oxygen (%)				
Treatment stratified by stage of COPD (yes or no)				
Outcomes				
Group Mean	Placebo	LABA	LABA-ICS	
FEV ₁ (% improvement)				
FVC (% improvement)				
HRQL score change				
Per patient per year				
Exacerbations (all stages)				
Exacerbation frequency (all stages)				
Exacerbation frequency (mild) compared to placebo				
Exacerbation frequency (moderate) oral steroid use				
Exacerbation frequency (severe)				
Time to first exacerbation (all stages)				
Time to first exacerbation (mild)				
Time to first exacerbation (moderate)				
Time to first exacerbation (severe)				
Exacerbations (stage 1)				
Exacerbation frequency (mild)				

Exacerbation frequency (moderate)			
Exacerbation frequency (severe)			
Time to first exacerbation (mild)			
Time to first exacerbation (moderate)			
Time to first exacerbation (severe)			
Exacerbations (stage 2)			
Exacerbation frequency (mild)			
Exacerbation frequency (moderate)			
Exacerbation frequency (severe)			
Time to first exacerbation (mild)			
Time to first exacerbation (moderate)			
Time to first exacerbation (severe)			
Exacerbations (stage 3)			
Exacerbation frequency (mild)			
Exacerbation frequency (moderate)			
Exacerbation frequency (severe)			
Time to first exacerbation (mild)			
Time to first exacerbation (moderate)			
Time to first exacerbation (severe)			
Mortality and Adverse Events			
Group Mean	Placebo	LABA	LABA/ICS
Mortality (all stages) (number)			
Mortality (stage 1)			
Mortality (stage 2)			
Mortality (stage 3)			
Treatment-specific adverse events			
Candidiasis			
Dysphonia			
Tachyarrhythmias			
Adrenal suppression			
Easy bruising			
Hypokalemia			
Other (list) COPD events			
Treatment-specific SAE (list) (%)			

HRQL=health-related quality of life; FVC=forced vital capacity; SD=standard deviation; SAE=specific adverse events; *dx=diagnosed.

APPENDIX 4: Search Strategy, Safety of Drugs

Databases	Limits	#	Keywords	Hits
Ovid Medline <1966 to March week 3 2005>	2000+ Performed March 30, 2005	1	copd.mp. or exp Pulmonary Disease, Chronic Obstructive	18690
		2	chronic obstructive pulmonary disease\$.mp.	9693
		3	chronic obstructive lung disease\$.mp.	2184
		4	or/1-3	24036
		5	exp ASTHMA/ or asthma.mp.	78764
		6	4 not 5	20741
		7	exp Adrenergic beta-Agonists/ or beta 2 agonist.mp.	86926
		8	long acting beta-2 agonist\$.mp.	266
		9	long acting bronchodilator\$.mp.	106
		10	formoterol.mp.	630
		11	salmeterol.mp.	1116
		12	foradil.mp.	31
		13	or/7-12	87150
		14	6 and 13	716
		15	corticosteroid\$.mp. or exp Adrenal Cortex Hormones/	160329
		16	13 and 15	111
		17	(salmeterol and fluticasone).mp.	221
		18	(budesonide and formeterol).mp.	1
		19	advair.mp.	24
		20	symbicort.mp.	36
		21	or/16-20	346
		22	6 and 21	128
		23	14 and 22	128
		24	adverse drug effect.mp.	58
		25	adverse event.mp.	3524
		26	safety.mp. or exp SAFETY/	119759
		27	safe.mp.	92173
		28	morbidity.mp. or exp MORBIDITY/	263862
		29	mortality.mp. or exp MORTALITY/	306785
		30	fatal outcome\$.mp. or exp Fatal Outcome/	27423
		31	or/24-30	673582
		32	31 and 23	25
		33	RANDOMIZED CONTROLLED TRIAL.pt.	197229
		34	CONTROLLED CLINICAL TRIAL.pt.	67598
		35	RANDOMIZED CONTROLLED TRIALS/	35750
		36	RANDOM ALLOCATION/	52373
		37	DOUBLE BLIND METHOD/	80261
		38	SINGLE-BLIND METHOD/	8668
		39	or/33-38	335026
		40	ANIMAL/ not HUMAN/	2835376
		41	39 not 40	316628
		42	CLINICAL TRIAL.pt.	398260
		43	exp CLINICAL TRIALS/	161892
		44	(clin\$ adj25 trial\$.ti,ab.	106387
		45	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.	79493
		46	PLACEBOS/	23418
		47	placebo\$.ti,ab.	86951
		48	random\$.ti,ab.	300817
		49	RESEARCH DESIGN/	39830
		50	or/42-49	708816
		51	50 not 40	658444

Databases	Limits	#	Keywords	Hits
		52	51 not 41	352312
		53	COMPARATIVE STUDY/	1167613
		54	exp EVALUATION STUDIES/	509447
		55	FOLLOW UP STUDIES/	293543
		56	PROSPECTIVE STUDIES/	182804
		57	(control\$ or prospectiv\$ or volunteer\$).ti,ab.	1497522
		58	or/53-57	2992613
		59	58 not 40	2293111
		60	59 not (41 or 53)	1832603
		61	41 or 53 or 60	2501543
		62	61 and 32	18
		63	limit 62 to yr=2000 - 2005	12
Ovid HealthStar <1975 to November 2004>	+2000 Search performed March 30, 2005	1	copd.mp. or exp Pulmonary Disease, Chronic Obstructive/	51817
		2	chronic obstructive pulmonary disease\$.mp.	6353
		3	chronic obstructive lung disease\$.mp.	1210
		4	or/1-3	53558
		5	exp ASTHMA/ or asthma.mp.	38158
		6	4 not 5	20719
		7	exp Adrenergic beta-Agonists/ or beta 2 agonist.mp.	18317
		8	long acting beta-2 agonist\$.mp.	170
		9	long acting bronchodilator\$.mp.	59
		10	formoterol.mp.	317
		11	salmeterol.mp.	600
		12	foradil.mp.	26
		13	or/7-12	18455
		14	6 and 13	838
		15	corticosteroid\$.mp. or exp Adrenal Cortex Hormones/	38681
		16	15 and 13	109
		17	(salmeterol and fluticasone).mp.	118
		18	(budesonide and formeterol).mp.	0
		19	advair.mp.	7
		20	symbicort.mp.	21
		21	or/16-20	232
		22	6 and 21	117
		23	14 and 22	117
		24	adverse drug effect.mp.	34
		25	adverse event.mp.	2949
		26	safety.mp. or exp SAFETY/	89064
		27	safe.mp.	68480
		28	morbidity.mp. or exp MORBIDITY/	232769
		29	mortality.mp. or exp MORTALITY/	262539
		30	fatal outcome\$.mp. or exp Fatal Outcome/	24284
		31	or/24-30	559482
		32	31 and 23	25
		33	RANDOMIZED CONTROLLED TRIAL.pt.	177859
		34	CONTROLLED CLINICAL TRIAL.pt.	47991
		35	RANDOMIZED CONTROLLED TRIALS/	31414
		36	RANDOM ALLOCATION/	37020
		37	DOUBLE BLIND METHOD/	79183
		38	SINGLE-BLIND METHOD/	7937
		39	or/33-38	279264
		40	ANIMAL/ not HUMAN/	380
		41	39 not 40	279263
		42	CLINICAL TRIAL.pt.	353429

Databases	Limits	#	Keywords	Hits
		43	exp CLINICAL TRIALS/	136774
		44	(clin\$ adj25 trial\$.ti,ab.	81324
		45	((singl\$ or doubl\$ or treb1\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.	72154
		46	PLACEBOS/	15556
		47	placebo\$.ti,ab.	71827
		48	random\$.ti,ab.	225735
		49	RESEARCH DESIGN/	40301
		50	or/42-49	558445
		51	50 not 40	558432
		52	51 not 41	288985
		53	COMPARATIVE STUDY/	555003
		54	exp EVALUATION STUDIES/	383015
		55	FOLLOW UP STUDIES/	258062
		56	PROSPECTIVE STUDIES/	170615
		57	(control\$ or prospectiv\$ or volunteer\$.ti,ab.	678758
		58	or/53-57	1537775
		59	58 not 40	1537594
		60	59 not (41 or 52)	1131089
		61	41 or 52 or 60	1699337
		62	61 and 33	16
		63	limit 64 to yr=2000-2005	6
EMBASE <1988 to 2005 week 13	+2000 Search performed March 30, 2005	1	copd.mp. or exp Chronic Obstructive Lung Disease/	17186
		2	chronic obstructive pulmonary disease\$.mp.	7916
		3	chronic obstructive lung disease\$.mp.	16879
		4	or/1-3	18152
		5	exp ASTHMA/ or asthma.mp.	60465
		6	4 not 5	14161
		7	exp Beta 2 Adrenergic Receptor Stimulating Agent/ or beta 2 agonist\$.mp.	5231
		8	long acting beta-2 agonist\$.mp.	54
		9	long acting bronchodilator.mp.	118
		10	exp Formoterol/ or formeterol.mp.	1639
		11	exp SALMETEROL/ or salmeterol.mp.	2853
		12	or/7-11	7625
		13	6 and 12	744
		14	corticosteroid\$.mp.	76448
		15	12 and 14	3256
		16	(salmeterol and fluticasone).mp.	676
		17	exp FLUTICASONE PROPIONATE PLUS SALMETEROL/	282
		18	(budesonide and formeterol).mp.	4
		19	exp BUDESONIDE PLUS FORMOTEROL/	154
		20	advair.mp.	84
		21	symbicort.mp.	127
		22	or/15-21	3634
		23	6 and 22	412
		24	13 and 23	404
		25	exp Drug Fatality/	3300
		26	exp Drug Safety/	75807
		27	exp FATALITY/	22597
		28	exp Drug Toxicity/	14347
		29	adverse drug event\$.mp.	504
		30	adverse event.mp.	3699
		31	safety.mp. or exp SAFETY/	112708

Databases	Limits	#	Keywords	Hits
		32	safe.mp.	74211
		33	morbidity.mp. or exp MORBIDITY/	103253
		34	exp MORTALITY/ or mortality.mp.	196602
		35	or/25-34	460563
		36	24 and 35	136
		37	Randomized Controlled Trial/	93240
		38	exp Randomization/	14191
		39	Double Blind Procedure/	50504
		40	Single Blind Procedure/	5189
		41	or/37-40	121734
		42	Clinical Trial/	326897
		43	(clin\$ adj25 trial\$.mp.	90144
		44	((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).mp.	61150
		45	exp Placebo/	50397
		46	(placebo\$ or random\$.mp.	309740
		47	exp Methodology/	698824
		48	exp Comparative Study/	129527
		49	exp Evaluation/	32169
		50	exp Follow Up/	149636
		51	exp Prospective Study/	44699
		52	(control\$ or prospectiv\$ or volunteer\$.mp.	2415356
		53	or/42-52	3064017
		54	41 or 53	3064017
		55	limit 54 to human	1965953
		56	Nonhuman/	2060166
		57	55 not 56	1758015
		58	36 and 57	106
		59	limit 58 to yr=2000 – 2005	97
Web of Science SCI Expanded; SSCI; A&HCI	Timespan= 2000-2005 Searched March 30, 2005	1	TS=(copd OR chronic obstructive pulmonary disease OR chronic oblstructive lung disease)	5498
		2	TS=(beta agonist* or long acting beta agonist* OR formoterol OR salmeterol)	1682
		3	#2 AND #1	244
		4	TS=(corticosteroid*)	13359
		5	#4 AND #2	478
		6	TS=((fluticasone AND salmeterol) OR (budesonide AND formoterol) OR advair OR symbicort OR steritide)	377
		7	#6 OR #5	634
		8	#7 AND #1	109
		9	#8 AND #3	109
		10	TS=(safety OR safe OR drug safety)	88317
		11	TS=(adverse event* OR aderesse drug event* OR durg fatality OR drug toxicity OR fatal outcome*)	13881
		12	TS=(morbidity OR mortality)	>100,000
		13	#10 AND #9	16
		14	#11 AND #9	10
		15	#12 AND #9	13
		16	#15 OR #14 OR #13	31

Databases	Limits	#	Keywords	Hits
EBM Reviews - Cochrane Database of Systematic Reviews <1st Quarter 2005>	+2000 Search performed March 24, 2005	1	copd.mp.	135
		2	chronic obstructive pulmonary disease\$.mp.	130
		3	chronic obstructive lung disease\$.mp.	13
		4	or/1-3	172
		5	asthma.mp.	338
		6	4 not 5	65
		7	beta 2 agonist\$.mp.	66
		8	long acting beta-2 agonist\$.mp.	15
		9	long acting bronchodilator\$.mp.	11
		10	formoterol.mp.	23
		11	salmeterol.mp.	32
		12	or/7-11	83
		13	6 and 12	2
		14	corticosteroid\$.mp.	540
		15	14 and 12	70
		16	(salmeterol and fluticasone).mp.	15
		17	(budesonide and formeterol).mp.	2
		18	advair.mp.	3
		19	ymbicort.mp.	3
		20	steritide.mp.	0
		21	or/15-20	71
		22	13 and 21	0
		23	(safety or safe or drug safety).mp.	1487
		24	(morbidity or mortality).mp.	2069
		25	(adverse event\$ or adverse drug event\$ or drug fatality or drug toxicity or fatal outcome\$.mp.	1367
		26	or/23-25	2978
		27	22 and 26	0
Ovid EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2005>	Search performed March 30, 2005 +2000	1	copd.mp.	2313
		2	chronic obstructive pulmonary disease\$.mp.	1554
		3	chronic obstructive lung disease\$.mp.	658
		4	or/1-3	3212
		5	asthma.mp.	12472
		6	4 not 5	2875
		7	beta 2 agonist\$.mp.	642
		8	long acting beta-2 agonist\$.mp.	111
		9	long acting bronchodilator\$.mp.	36
		10	formoterol.mp.	665
		11	salmeterol.mp.	960
		12	or/7-11	2013
		13	6 and 12	266
		14	corticosteroid\$.mp.	4769
		15	14 and 12	349
		16	(salmeterol and fluticasone).mp.	263
		17	(budesonide and formeterol).mp.	10
		18	advair.mp.	12
		19	ymbicort.mp.	65
		20	steritide.mp.	0
		21	or/15-20	607
		22	13 and 21	54
		23	(safety or safe or drug safety).mp.	32343
		24	(morbidity or mortality).mp.	14762
		25	(adverse event\$ or adverse drug event\$ or drug fatality or drug toxicity or fatal outcome\$.mp.	11488

Databases	Limits	#	Keywords	Hits
		26	or/23-25	50522
		27	22 and 26	9
		28	limit 27 to yr=2000 – 2004	6
EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2005>	Search performed March 30, 2005	1	copd.mp.	31
		2	chronic obstructive pulmonary disease\$.mp.	50
		3	chronic obstructive lung disease\$.mp.	2
		4	or/1-3	55
		5	asthma.mp.	116
		6	4 not 5	40
		7	beta 2 agonist\$.mp.	3
		8	long acting beta-2 agonist\$.mp.	1
		9	long acting bronchodilator\$.mp.	0
		10	formoterol.mp.	3
		11	salmeterol.mp.	7
		12	or/7-11	11
		13	6 and 12	1
		14	corticosteroid\$.mp.	107
		15	14 and 12	4
		16	(salmeterol and fluticasone).mp.	4
		17	(budesonide and formeterol).mp.	0
		18	advair.mp.	0
		19	symbicort.mp.	0
		20	steritide.mp.	0
		21	or/15-20	5
		22	13 and 21	0
		23	(safety or safe or drug safety).mp.	544
		24	(morbidity or mortality).mp.	863
		25	(adverse event\$ or adverse drug event\$ or drug fatality or drug toxicity or fatal outcome\$.mp.	339
		26	or/23-25	1423
		27	22 and 26	0
Toxline	2000-2005 Search performed March 30, 2005	1	copd or (chronic obstructive pulmonary disease*) or (chronic obstructive lung disease*)	482
		2	(long acting beta agonist*) or (beta agonist*) or salmeterol or formoterol	223
		3	fluticasone or budesonide or advair or symbicort	458
		4	(adverse drug effect) or (adverse event) or safety) or (safe or morbidity or mortality) or (fatal outcome)	38824
		5	(randomized controlled trial*) or (clinical trial*) or (random allocation)) or ((double blind method) or (systematic review) or meta-analysis	36975
		6	#1 AND #2 AND #3 AND #4 AND #5	3
Ovid International Pharmaceutic al Abstracts <1970 to March 2005>	Search performed March 30, 2005 +2000	1	copd.mp.	343
		2	chronic obstructive pulmonary disease\$.mp.	559
		3	chronic obstructive lung disease\$.mp.	110
		4	or/1-3	742
		5	asthma.mp.	4107
		6	4 not 5	593
		7	beta 2 agonist\$.mp.	41
		8	long acting beta-2 agonist\$.mp.	2
		9	long acting bronchodilator\$.mp.	14
		10	salmeterol.mp.	211
		11	formoterol.mp.	100
		12	or/7-11	323

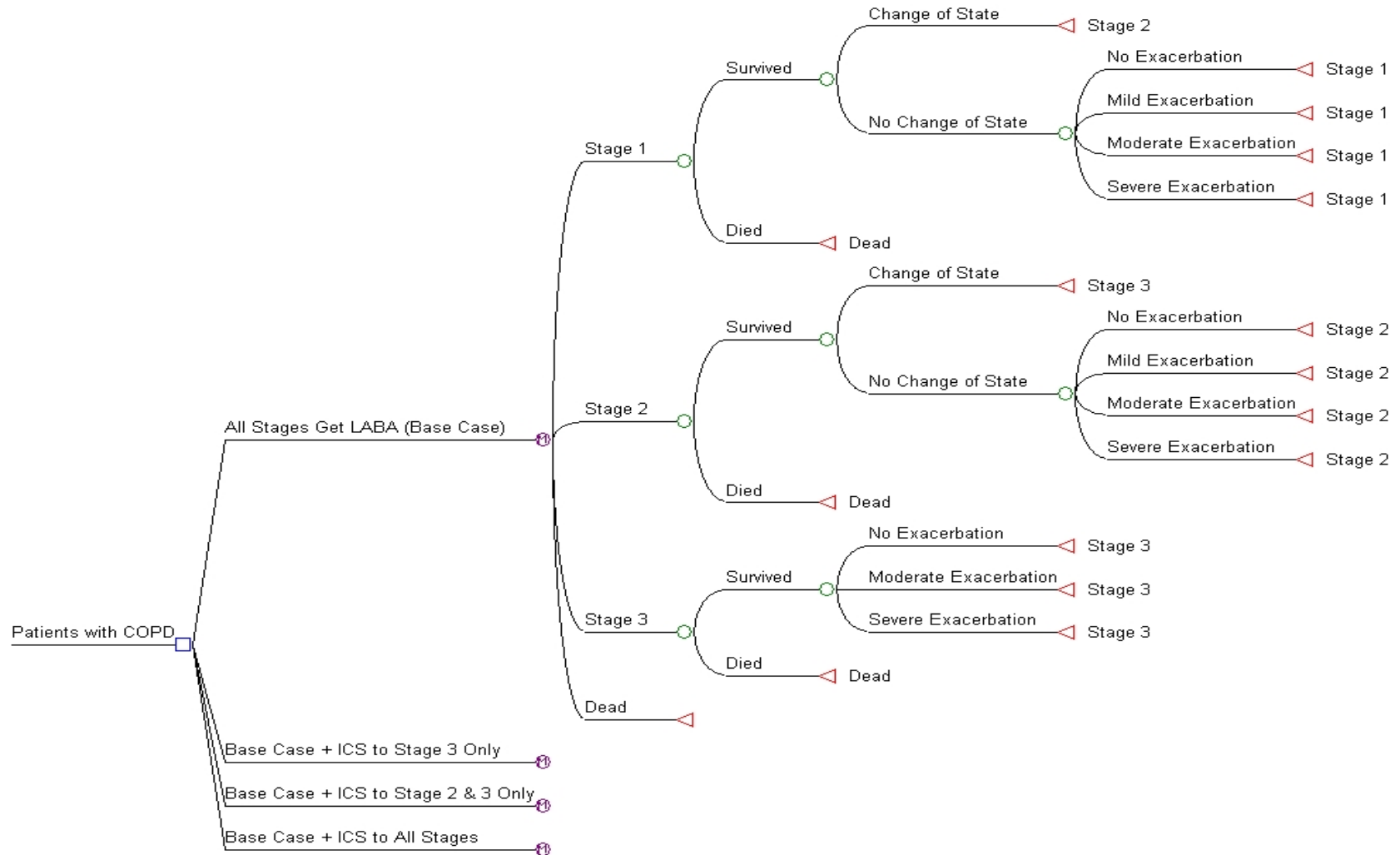
		13	6 and 12	32
		14	corticosteroid\$.mp.	4178
		15	14 and 12	70
		16	(salmeterol and fluticasone).mp.	56
		17	(budesonide and formeterol).mp.	0
		18	advair.mp.	8
		19	symbicort.mp.	7
		20	seritide.mp.	0
		21	or/15-20	106
		22	6 and 21	9
		23	13 or 22	9
		24	(safety or safe or drug safety).mp.	17011
		25	(adverse event\$ or adverse drug event\$ or drug fatality or drug toxicity or fatal outcome\$.mp.	4363
		26	(morbidity or mortality).mp.	6314
		27	or/24-26	25466
		28	23 and 27	3
		29	limit 28 to yr=2000 - 2005	3
CRD databases: DARE; NHS EED; HTA	Search performed March 30, 2005		(copd OR chronic obstructive pulmonary disease AND (long acting beta 2 agonist* OR fomoterol OR salmeterol) AND (fluticasone OR budesonide OR advair OR symbicort OR steritide) AND (safety OR safe OR morbidity OR mortality OR fatal outcome* OR adverse effect* OR adverse event*))	0

Total = 155

Duplicates = 37

Total Remaining = 118

APPENDIX 5: Markov Model Comparing Treatment Strategies for COPD



APPENDIX 6: Results of Included Studies

Results of included studies										
Study		Subject Randomized to Each Arm	Subjects Completed Each Arm	Mean FEV ₁ (baseline % pred)	Mean FEV ₁ Change (% improvement from baseline)	Mean HRQL Change (from placebo)	Exacerbation Frequency (annual rate per person)	Time to First Exacerbation	Mortality	Treatment – Specific Adverse Events
Calverly ¹⁶	placebo	361	221	44.2%	mL change versus placebo	N/A	moderate: 0.76 severe: 1.3	not assessed	not reported	14%
	fluticasone	372	253	44.3%	73 mL	-1.1	moderate: 0.54 severe: 1.04	not assessed	not reported	12%
	salmeterol+ fluticasone	358	269	44.8%	133 mL	-2.2	moderate: 0.46 severe: 0.97	not assessed	not reported	16%
Calverly ¹⁴	placebo	256	150	36%	% improvement from placebo	N/A	moderate: 1.14 severe: 1.8	96 days	5 deaths	5/1000 treatments days
	formoterol	255	144	36%	5%	-4.1	moderate: 0.91 severe: 1.85	154 days	13 deaths	6/1000
	formoterol+ budesonide	254	180	36%	14%	-7.5	moderate: 0.63 severe: 1.38	254 days	5 deaths	5/1000 treatment days
Szafranski ¹⁵	placebo	205	115	36%	% improvement from placebo	mean change from baseline -0.03	moderate: 1.07 severe: 1.87	not assessed	9 deaths	COPD events 26%
	formoterol	201	137	36%	14% (formoterol)	-3.6	moderate: 1.04 severe: 1.84	not assessed	6 deaths	19%
	formoterol+ budesonide	208	149	36%	15% (formoterol+ budesonide)	-3.9	moderate: 0.74 severe: 1.42	not assessed	6 deaths	17%

HRQL=health-related quality of life; N/A=not applicable.