Supplementary material

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1 Targeted literature review

The steps followed to conduct the targeted literature review (TLR), adhere to the guidelines published by the Cochrane Collaboration for systematic literature review (SLR)[1]. However, a reminder that a TLR tend to be more pragmatic than SLR. The TLR followed four core stages: a) Definition of the scope of search and agreement of search (Table 1;Table 2); b) Implementation of searches strategies and abstract review to inform included papers (Table 2; Figure 1); c) Selection of priority articles and desk search (sections 1.2, 1.3); d) Data extraction and reporting.

1.1 OVID search

The TLR was developed using the electronic literature databases through OVID. The OVID platform is a search platform that provides standardised access to a wide range of literature databases (all Medline (R), all Embase and all Evidence Based Medicine (EBM) review databases). The timeframe of the search was restricted to the last 10 years (2006-2016). The search strings and their relationships using Boolean terms define the searches for each area of evidence (disease, intervention, utility, economic, comorbidities and effects). Search strings were filtered in titles only and strategies were identical across the databases. A summary of the scope and search strategy is provided in Table 1 and Table 2.

1.2 Additional search

To complement the step described above, additional non-systematic searches was conducted: either by selecting specific studies referenced in the list of references of priority articles, either searching in database publications of International Society of Pharmacoeconomics and Outcomes Research (ISPOR US and EU) (note that last years are included in Medline and are as such covered) or in grey Google literature.

1.3 Results

Figure 1 depicts the flow of information through the different phases of the TLR and Table 3 list all the selected studies found and analysed in this TLR.

2 References

1. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].The Cochrane Collaboration, 2011. [Internet]. The Cochrane Collaboration; 2011 [cited 2018 Jun 25]. Available from: http://handbook-5-1.cochrane.org/

3 Tables

Table 1: Scope of the search strategies

Name	Efficacy and effects	Economic studies	HRQoL (utility)
Databases	The OVID platform (which includes all Medline (R), all Embase and all Evidence Based Medicine (EBM) review databases		
Patient population	COPD patients (either stable patients or hospitalized due to an exacerbation)		
Intervention	Physical exercise/activity or pulmonary rehabilitation		
Comparators	Sedentary life style, no pulmonary rehabilitation, natural course of COPD		
Outcome measures	Spirometry, lung function capacity, exercise capacity, severity classification, survival and mortality	Reported resource use and cost parameters, incremental cost-effectiveness ratio (ICER)	Reported HRQoL scores, utility or dis(utility)
Study design	• RCTs (all head-to-head or placebo controlled studies using single or combination therapies) • Non-RCTs: trials or observational studies where participants were assigned by investigators non-randomly to treatment group(s)	• Costs studies • Resource use studies • Economic evaluations	• Utility and HRQoL studies **OR** • Economic evaluations using utility measures
Restrictions	• Language: English and Spanish • Publication year: 2006-2016 • No case reports study • Country: Any		
Inclusion	• Providing quantitative impact of exercise • On key COPD outcomes: spirometry (e.g.: FEV1), exercise capacity (e.g. 6MWT, CPET, ESWT), muscle strength, dyspnea (MRC), mortality, QoL/PRO (SGRQ, EQ-5D, CRDQ) or COPD burden (hospitalization, costs, ICER)		
Exclusion	• Population: no COPD or specific subgroups of COPD patients (e.g. obesity) • Intervention: not related to exercise • Outcomes: qualitative, measured during the physical exercise • Design: general (non-systematic) review or study protocol without results		

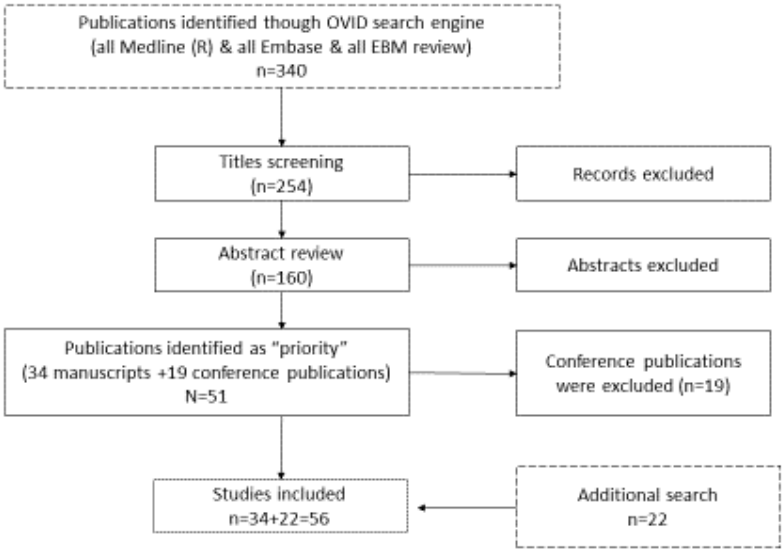
HRQoL - Health-related quality of life; RCT – Randomized control trial; ICER - Incremental cost-effectiveness ratio; COPD- Chronic Obstructive Pulmonary Disease; FEV1: forced expiratory volume in 1 second; 6MWT: 6-minute walking test; ICER: incremental cost-effectiveness ratio; MRC: Medical Research Council dyspnea scale; CPET- Cardio pulmonary exercise testing; ESWT- endurance shuttle walk test, QOL-Quality of Life; PRO - Patient-Reported Outcomes; SGRQ - St. George's Respiratory Questionnaire; EQ-5D- EuroQol five dimensions questionnaire; CRDQ - Chronic Respiratory Disease Questionnaire

Table 2: Search terms and strategy

Index	Thematic group	Search words	Number of hits (N)
#	**Disease**		
1		Chronic obstructive pulmonary disease OR COPD	79904
	Intervention		
2		Physical activity OR exercise OR sport OR training OR inactivity OR sedentary	
3		**#1 and #2**	5954
4		Rehabilitation	
5		**(#3 or 4#)**	**8032**
	Utility		
6		Quality of life OR Utility OR Qol	
7		**#5 and #6**	374
8		EQ-5D OR SF-36 OR SF-6D	
9		**#5 and (#6 or #8)**	376
		Saint George Respiratory Questionnaire	
		Mahler's dyspnea index	
		London Chest Activity of Daily Living scale	
		Scales for quality of well-being	
11		6 minute walking test	
12		**#5 and (#11 or #9)**	383
13		Health status or Health state	
14		**#5 and (#13 or #12)**	454
	Economic		
15		Economic OR Cost OR Burden	
16		**#5 and #15**	52
17		Hospitalization	
		#5 and (#15 or #17)	92
	Comorbidities and effects		
18		Comorbidity	
19		Cardiovascular disease	
20		Diabetes	
21		Heart failure	
22		Hypertension	
23		Obesity	
24		**#5 and (#18 or #19 or #20 or #21 or #22 or #23)**	177
25		Symptoms OR severity or GOLD or Global Initiative for Chronic Obstructive Lung Disease OR Progression OR Bronchodilation	
26		Lung function capacity	117
27		**#5 and (#26 or # 25)**	250
28		Survival OR Mortality	
29		**#5 and # 28**	85
	Union of all searches		*680*
	Union of all searches after removing duplicates		*448*
	Limiting to 2006 – 2016		*340*

First column presents the historical index in OVID for the conducted searches. In some cases, indexes reflect a combination of previous searches. Second and third columns represent the thematic group and related search strings, and the fourth column represent the total number of studies/hits found by OVID.

Figure 1: Prisma diagram



57 **Table 3: List of priority articles**

#	Study
1	Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available from: http://goldcopd.org.
2	Ali MS, Talwar D, Jain SK.The effect of a short-term pulmonary rehabilitation on exercise capacity and quality of life in patients hospitalised with acute exacerbation of chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci. 2014;56(1):13-9.
3	Atsou K., Crequit P. Chouaid C, Hejblum G. Simulation-Based Estimates of the Effectiveness and Cost-Effectiveness of Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease in France. PLoS One. 2016; 11(6): e0156514.
4	Bratås O, Espnes GA, Rannestad T, Walstad R. Pulmonary rehabilitation reduces depression and enhances health-related quality of life in COPD patients--especially in patients with mild or moderate disease. Chron Respir Dis. 2010;7(4):229-37
5	Briggs A, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, Exuzides A, Colby C, Tabberer M, Muellerova H, Locantore N, Rutten van-Mölken MP, Lomas DA. Development of the Galaxy Chronic Obstructive Pulmonary Disease (COPD) Model Using Data from ECLIPSE: Internal Validation of a Linked-Equations Cohort Model. Med Decis Making. 2017;37(4):469-480.
6	Briggs A, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, Exuzides A, Colby C, Tabberer M, Muellerova H, Locantore N, Rutten van-Mölken MP, Lomas DA. Development of the Galaxy Chronic Obstructive Pulmonary Disease (COPD) Model Using Data from ECLIPSE: Internal Validation of a Linked-Equations Cohort Model. Med Decis Making. 2016.
7	Burns DK, Wilson EC, Browne P, Olive S, Clark A, Galey P, Dix E, Woodhouse H, Robinson S, Wilson A. The Cost Effectiveness of Maintenance Schedules Following Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease: An Economic Evaluation Alongside a Randomised Controlled Trial. Appl Health Econ Health Policy. 2016;14(1):105-15.
8	Hailey D, Jacobs P, Stickland M, Chuck A, Marciniuk DD, Mayers I, Mierzwinsky-Urban M. Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease: Clinical, Economic, and Budget Impact Analysis [Technology report number 126]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2010 (CADTH report)
9	Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–89. (TORCH)
10	Corhay JL1, Louis R. The UPLIFT study (Understanding Potential Long-term Impacts on Function with Tiotropium). Rev Med Liege. 2009 Jan; 64(1):52-7.
11	Da Silva GP, Morano MT, Cavalcante AG, De Andrade NM, Daher Ede F, Pereira ED. Exercise capacity impairment in COPD patients with comorbidities. Rev Port Pneumol (2006). 2015;21(5):233-8.(abstract)
12	Dürr S., Zogg S., Miedinger D.,Steveling E. H, Maier S. Leuppi J.D. Daily Physical Activity, Functional Capacity and Quality of Life in Patients with COPD. COPD. 2014:11(6):689-96..
13	Enfield K, Gammon S, Floyd J, Falt C, Patrie J, Platts-Mills TA, Truwit JD, Shim YM. Six-minute walk distance in patients with severe end-stage COPD: association with survival after inpatient pulmonary rehabilitation. J Cardiopulm Rehabil Prev. 2010;30(3):195-202.
14	Esteban C, Quintana JM, Aburto M, Moraza J, Egurrola M, Pérez-Izquierdo J, Aizpiri S, Aguirre U, Capelastegui A.Impact of changes in physical activity on health-related quality of life among patients with COPD. Eur Respir J. 2010;36(2):292-300.
15	Esteban C, Arostegui I, Aburto M, Moraza J, Quintana JM, Aizpiri S, Basualdo LV, Capelastegui A.Influence of changes in physical activity on frequency of hospitalization in chronic obstructive pulmonary disease. Respirology. 2014;19(3):330-8
16	Esteban C, Garcia-Gutierrez S, Legarreta MJ, Anton-Ladislao A, Gonzalez N, Lafuente I, Fernandez de Larrea N, Vidal S, Bare M, Quintana JM -Copd Group I. One-year Mortality in COPD After an Exacerbation: The Effect of Physical Activity Changes During the Event. COPD. 2016;13(6):718-725

17	Exuzides A, Colby C, Briggs A, Lomas DA, Rutten van-Mölken M, Tabberer M, Chambers M, Muellerova H, Locantore N, Risebrough NA, Ismaila AS, Gonzalez-McQuire S. Statistical Modeling of Disease Progression for Chronic Obstructive Pulmonary Disease Using Data from the ECLIPSE Study. Med Decis Making. 2017;37(4):453-468
18	Foglio K, Bianchi L, Bruletti G, Porta R, Vitacca M, Balbi B, Ambrosino N. Seven-year time course of lung function, symptoms, health-related quality of life, and exercise tolerance in COPD patients undergoing pulmonary rehabilitation programs. Respir Med. 2007;101(9):1961-70. Epub 2007 May 24.
19	Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax. 2006;61(9):772-8.
20	Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM.Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am J Respir Crit Care Med. 2007;175(5):458-63.
21	Gillespie P, O'Shea E, Casey D, Murphy K, Devane D, Cooney A, Mee L, Kirwan C, McCarthy B, Newell J; PRINCE study team. The cost-effectiveness of a structured education pulmonary rehabilitation programme for chronic obstructive pulmonary disease in primary care: the PRINCE cluster randomised trial. BMJ Open. 2013;3(11):e003479.
22	Hakamy A, Bolton CE, McKeever TM.The effect of pulmonary rehabilitation on mortality, balance, and risk of fall in stable patients with chronic obstructive pulmonary disease. Chron Respir Dis. 2017;14(1):54-62.
23	Hoogendoorn M, Talitha L. Feenstra, Yumi Asukai, Andrew H. Briggs, Ryan N. Hansen, Reiner Leidl, Nancy Risebrough, Yevgeniy Samyshkin, Margarethe Wacker, Maureen P. Rutten-van Mölken. External Validation of Health Economic Decision Models for Chronic Obstructive Pulmonary Disease (COPD): Report of the Third COPD Modeling Meeting. Value In Health; 2017;20: 397-403
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29	McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2015;2: CD003793.
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31	Miravitlles M, Gáldiz JB, Huerta A, Villacampa A, Carcedo D, Garcia-Rio F. Cost-effectiveness of combination therapy umeclidinium/vilanterol versus tiotropium in symptomatic COPD Spanish patients. Int J Chron Obstruct Pulmon Dis. 2016;11:123-32.
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